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BENZODIAZEPINE DISCONTINUATION TREATMENT IN OUTPATIENTS WITH COMPLICATED DEPENDENCE

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Academic dissertation

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CONTENTS

ABBREVIATIONS

AMT	Anxiety management training
ANCOVA	Analysis of covariance
APA	American Psychiatric Association
AUDIT	Alcohol Use Disorders Identification Test
BZ	Benzodiazepine
CBT	Cognitive-behavioral treatment
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
CMT	Complaints management training
CNS	Central nervous system
CYP	Cytochrome P450
DDD	Defined daily dose
df	Degrees of freedom
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, third edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, third edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
ECA	Epidemiological Catchment Area Study
GABA	Gamma-aminobutyric acid
GGT	Gamma-glutamyltransferase
GLM	General linear model
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale
HRQOL	Health-Related Quality of Life
HSCL	Hopkins Symptom Checklist
ICD	International Classification of Diseases
ICD-10	International Classification of Diseases, tenth edition
Kela	Social Insurance Institution
MANCOVA	Multivariate analysis of covariance
MOS SF-36	Medical Outcome Study SF-36 Health Survey
NCS	National Comorbidity Survey
NOS	Not otherwise specified
OR	Odds ratio
p.r.n.	As needed (Latin pro re nata)
RAND-36	RAND 36-Item Health Survey
SCID	Structured Clinical Interview
SCID-P	Structured Clinical Interview, Patient Version
SCID-II	Structured Clinical Interview for Personality Disorders
SCL-90	Symptom Checklist-90
SD	Standard deviation
SDS	Severity of Dependence Scale
SOFAS	Social and Occupational Functioning Assessment Scale
STAKES	National Research and Development Center for Welfare and Health
VAS	Visual analogue scale
WHO	World Health Organization

DEFINITIONS OF FREQUENTLY USED TERMS

Abuse - abuse was defined according to the DSM-III-R classification system (see Table 2);

Addiction - a term used in neurobiology refering to a disorder in humans characterized by compulsive drug use and loss of control over drug intake (Koob and Le Moal, 1997);

Anxiolytic - a drug that reduces anxiety;

Behavioral therapy - clinical applications of the principles developed in learning theory, e.g. graded exposure (Sadock and Sadock, 2003b);

Cognitive therapy - approaches based on an underlying theoretical rationale that an individual's affect and behavior are largely determined by the way in which he structures the world (Sadock and Sadock, 2003b). The components are didactic aspects, cognitive techniques (e.g. eliciting and testing automatic thoughts, identifying and testing the validity of maladaptive assumptions), and behavioral techniques;

Complicated dependence - complicated benzodiazepine dependence was defined as use of benzodiazepines exceeding usual therapeutic doses (>40 mg/day in diazepam equivalents), as concomitant lifetime or current alcohol use disorders, or as concomitant hazardous and harmful alcohol use as defined by the Alcohol Use Disorders Identification Test (AUDIT);

Dependence - dependence was defined according to the DSM-III-R classification system (see Table 2);

Hypnotic - a drug used to induce sleep;

Misuse - definitions of benzodiazepine misuse vary. The American Psychiatric Association (APA, 1990) defined unsupervised benzodiazepine use as 1) occasional self-medication; 2) intake of a therapeutic dose on a regular basis for symptom relief, but without medical supervision; and 3) self-medicating for symptom relief with higher than usual therapeutic doses. Of these, the latter two categories constituted true misuse. Recreational use of benzodiazepines was termed abuse, overlapping with the definition of abuse in diagnostic classifications. Here, benzodiazepine misuse was defined as use outside medical supervision. In practice, this included subjects who self-medicated their symptoms with doses higher than prescribed or who used benzodiazepines for different purposes than prescribed or went to several prescribers, who used benzodiazepines to self-medicate symptoms related to alcohol use, or who used benzodiazepines for recreational purposes in connection with alcohol use. Thus, the concept of misuse in this study follows the definition of APA, but also includes subjects who used benzodiazepines as intoxicants;

Sedative - a drug that reduces subjective tension and induces mental calmness; virtually the same as an anxiolytic (Sadock and Sadock, 2003a). In high doses, sedatives and anxiolytics can induce sleep, and in low doses, hypnotics induce daytime sedation. Anxiolytic and sedative-hypnotic agents include benzodiazepines, nonbenzodiazepine agonists that act at the benzodiazepine receptor (e.g. zopiclone), barbiturates, and some other barbiturate-like substances.

ABSTRACT

Characteristics of subjects with benzodiazepine dependence typically complicated by harmful and hazardous alcohol use or high benzodiazepine doses are described. The effectiveness of gradual benzodiazepine taper combined with cognitive-behavioral treatment and carried out in a natural treatment setting was compared with the usual treatment used for dependence problems in outpatient clinics consisting of mainly supportive approaches. The subjects were monitored after withdrawal treatment to evaluate long-term outcome and predictors of remaining benzodiazepine-free.

The study was designed as a randomized, controlled clinical trial. Seventy-six subjects with benzodiazepine dependence (DSM-III-R) participated at four public sector outpatient alcohol and drug dependence clinics (A-clinics) in Helsinki.

No significant between-group differences were found in subjects' baseline measures. The median benzodiazepine dose was 35 mg in diazepam equivalents (mean 45 mg, SD = 35.5, range 2.5 to 180) and the median duration of benzodiazepine use was 84 months (mean 116, SD = 84.2, range 8 to 360). Thirty percent had a current and 64% a lifetime alcohol use disorder, 49% a current anxiety disorder, 45% a current depressive disorder, and 64% a personality disorder. Hazardous or harmful alcohol use defined by the Alcohol Use Disorders Identification Test (AUDIT) was found in 63% of the subjects.

No significant differences in outcomes were observed between the groups. A total of 13% of the experimental group and 27% of the control group were able to discontinue drug use. In addition, 67% of the experimental group and 57% of the control group were able to decrease the dose. At the end of the follow-up, 18% and 32%, respectively, were benzodiazepine-free. Subjects with lower benzodiazepine doses and no previous withdrawal attempts succeeded better in benzodiazepine discontinuation. The same variables, plus high life satisfaction, predicted staying benzodiazepine-free. Energy/vitality, home management, and life satisfaction scores for subjects with clinically significant (over 50%) benzodiazepine dose decreases improved more than those for subjects with smaller decreases.

In conclusion, in subjects with complicated benzodiazepine dependence, the benefits of withdrawal treatment may persist, and clinically significant dose decreases were associated with improvements in health-related quality of life.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by Roman numerals I-IV:

I Vorma H, Naukkarinen H, Sarna S, Kuoppasalmi K. Treatment of out-patients with complicated benzodiazepine dependence: comparison of two approaches. Addiction 2002;97:851-859.

II Vorma H, Naukkarinen HH, Sarna SJ, Kuoppasalmi KI. Predictors of benzodiazepine discontinuation in subjects with complicated dependence. Substance Use and Misuse. Accepted for publication.

III Vorma H, Naukkarinen H, Sarna S, Kuoppasalmi K. Long-term outcome after benzodiazepine withdrawal treatment in subjects with complicated dependence. Drug and Alcohol Dependence 2003;70:309-314.

IV Vorma H, Naukkarinen H, Sarna S, Kuoppasalmi K. Symptom severity and quality of life after benzodiazepine withdrawal treatment in subjects with complicated dependence. Addictive Behaviors. Accepted for publication.

In addition, some unpublished data have been included. The original publications have been reproduced with permission from the copyright holders.

1. INTRODUCTION

Anxiety is a signal of impending danger, the purpose of which is to improve an individual's chances of survival. However, when symptoms of anxiety are pronounced in relation to its triggers or when no actual threat exists, anxiety is considered pathological. Through history, humans have relieved symptoms of anxiety by using psychoactive substances such as alcohol and opium. The same substances have also been used as intoxicants (Medawar, 1992).

From the middle of the 19th century onwards, anxiolytic medications have been developed. Chloral hydrate was introduced as a sedative-hypnotic. Bromides were initially used for conditions that today would be treated by anxiolytics and antidepressants. Barbiturates were synthesized in the early 20th century. Meprobamate and such drugs as methyprylon, ethchlorvynol, and gluthedimide were introduced as alternatives to barbiturates in the 1950s. All of these drugs were toxic and carried a risk of dependence. Chronic intoxication (bromism), including restlessness, disorientation, paranoid trends, and hallucinations, resulted from continuous bromide treatment, and barbiturates were associated with fatal accidents, suicide, and barbiturate-type dependence. Benzodiazepines (BZs) largely replaced these earlier medications by the end of the 1960s (Medawar, 1992).

The first BZ compound, chlordiazepoxide, was introduced to the market as a tranquillizer in 1960 and the second, diazepam, followed in 1963 (Lader, 1993). Compared with earlier anxiolytic medications, BZs were safe; they had minimal toxicity and a good tolerability. Accordingly, they soon became the most highly prescribed psychoactive drugs in the world (Fraser, 1998).

BZs are anticonvulsive, centrally muscle-relaxing, sedative/hypnotic, and anxiolytic agents (Syvälahti and Hietala, 2001). Therefore, they are used for a wide range of psychiatric and medical indications, including sleep disorders (Holbrook et al., 2000; Roth et al., 2001; Smith et al., 2002), alcohol withdrawal syndrome (Williams and McBride, 1998a; Holbrook et al., 1999), most anxiety disorders (Argyropoulos and Nutt, 1999; Leinonen et al., 2000), cerebral seizures, epilepsy, central spasticity, muscle tension, and various applications in anesthesiology and emergency medicine (Möller, 1999). Benzodiazepine abuse is common in subjects with alcohol problems, along with appropriate use (Ciraulo et al., 1988; Ross, 1993). Benzodiazepines are extensively used as intoxicants and for self-medication in the contexts of multiple substance abuse and opiate abuse (Griffiths and Weerts, 1997).

The adverse effects of BZs include drowsiness, dizziness, ataxia, mild cognitive deficits, anterograde amnesia, and paradoxical reactions (Sadock and Sadock, 2003a). BZ potency is limited by the availability of the neurotransmitter gamma-aminobutyric acid (GABA). This property, plus the absence of BZ receptors associated with the peripheral nervous system, may account for the safety of BZs, as they have little effect upon cardiovascular, respiratory, gastrointestinal, or genitourinary systems (Feldman et al., 1997b). Alcohol and other sedative-hypnotic compounds add to the sedative effects of BZs. They serve as ligands for a greater range of receptor sites, thereby raising the possibility of severe toxic effects (Feldman et al., 1997b).

The most serious adverse effect of BZs is dependence. Soon after the first BZ, chlordiazepoxide, was introduced to the market, withdrawal symptoms were observed with very high doses (300 to 600 mg/day) (Hollister et al., 1961). Later, case reports documented physiological dependence in patients who had increased their doses above the recommended therapeutic limits (Peters and Boeters, 1970; Venzlaff, 1972; Woody et al., 1975, Bliding, 1978). Dependence on therapeutic dose was first noticed in the 1970s (Covi et al., 1973), but

was concluded to occur rarely under conditions of clinical use (Marks, 1978). In the 1980s, the concept of therapeutic-dose dependence was established (Marks, 1983; Owen and Tyrer, 1983; Ashton, 1984). Studies involving mostly chronic therapeutic-dose BZ users (Rickels et al., 1999) and panic disorder patients (Spiegel, 1999) established the prevailing approaches of BZ withdrawal treatment, gradual dose taper and cognitive-behavioral treatment.

Benefits and risks of continued BZ treatment should be weighed, recognizing that some patients may do better without long-term treatment, whereas others may continue to benefit (Woods et al., 1992). The available scientific information is scant. Evidence does, however, exist that patients who discontinue long-term BZ use may attain lower levels of psychiatric symptoms (Rickels et al., 1991; Rickels et al., 2000). Detoxification from BZ dependence may reduce outpatient medical and psychiatric health service use (Burke et al., 1995). Some studies have suggested that chronic BZ users may in fact be treating dependence rather than the initial psychiatric symptoms (Cappell et al., 1987) or that low-dose users may develop a craving for medication even before any dependence syndrome is observed (Linden et al., 1998). Other studies have suggested long-lasting benefits from BZs (Cowley et al., 1995). Therefore, the risk of physiological dependence has been deemed not to be sufficient to prohibit long-term use (Woods et al., 1992). Case reports have shown that some anxiety-disordered patients have required long-term BZ treatment with higher than normal doses to make gains from any treatment, even if they were physiologically dependent on them (Huttunen, 2002). Furthermore, while subjects with current substance use disorders are at increased risk of developing BZ dependence, a history of substance abuse may not be a major risk factor for future BZ abuse or dependence (Posternak and Mueller, 2001). No consensus has yet been reached regarding the appropriateness and safety of long-term BZ use (Fraser, 1998; Williams and McBride, 1998; Lader, 1999).

The present study was designed to investigate the effects of a BZ withdrawal treatment program in subjects with complicated dependence (i.e. the majority were taking high BZ dosages or had concurrent alcohol problems) in a natural outpatient treatment setting. A cognitive-behavioral approach was compared with traditional treatment combined with gradual BZ taper. The psychopathology and health-related quality of life of the subjects as well as the predictors of discontinuing BZs and staying BZ-free were evaluated.

2. REVIEW OF THE LITERATURE

2.1. Benzodiazepine pharmacology

The term benzodiazepine is derived from a benzene ring being fused to a 1,4-diazepine ring (Feldman et al., 1997b). BZ compounds also contain other substituent rings. More than fifty BS derivatives are marketed for clinical use worldwide. The most significant are diazepam, lorazepam, alprazolam, temazepam, chlordiazepoxide, nitrazepam, triazolam, flunitrazepam, and lormetazepam (the latter two agents are not marketed in Finland) (United Nations, 1997).

All BZ derivatives possess anxiolytic, sedative, hypnotic, anticonvulsant, and muscle-relaxant effects, but their relative potency in these categories varies. However, when patients are changed from one BZ to another of an equivalent dosage under double-blind conditions, almost complete cross-dependence has been demonstrated (Tyrer, 1993). The affinity with which BZs bind to receptors varies, the most potent BZs being triazolam, midazolam, clonazepam, lorazepam, alprazolam, and diazepam (Tyrer, 1993).

Depending on their lipid-solubility, BZs may cross the blood-brain barrier into the central nervous system (CNS). The time taken for this transfer from vascular space to the CNS represents the onset of action. High lipid-soluble drugs like diazepam have a faster onset of action (and time to peak plasma level; see Table 1), whereas less lipid-soluble agents like oxazepam have a slower onset of action. Duration of action is dependent on the redistribution of the drug from the CNS to the peripheral fat stores and the hepatic metabolism of the drug. Prolonged administration of BZs leads to saturation of the peripheral fat stores for the more lipid-soluble agents. As these stores become saturated, they serve as sites of leaching of the drug and active metabolites (Bailey et al., 1994).

BZs are metabolized through a variety of hydroxylation, desalkylation, reduction, and acetylation reactions (phase I reactions), followed in many cases by conjugation to glucuronic acid (phase II) before excretion (United Nations, 1997). In most cases, the phase I metabolites have biological activity. Several BZs may be considered pro-drugs, which are rapidly metabolized into active metabolites. The main metabolites are presented in Table 1. Cytochrome P450 (CYP) enzymes in the liver are responsible for phase I drug metabolism. Phase II metabolism is less affected by liver disease and old age (Bailey et al., 1994; Pollock, 1998). Only alprazolam, midazolam, and triazolam have clinically important metabolic drug interactions with other medications (Pollock, 1998).

BZs can be classified as short-acting (half-life less than 10 hours), intermediate-acting (10-24 hours), and long-acting (more than 24 hours) (United Nations, 1997) (Table 1). The duration of action depends not only on the elimination half-life of the drug itself but also on active metabolites.

2.2. Effects and clinical use of benzodiazepines

The pharmacologic properties of BZs are anticonvulsive, centrally muscle-relaxing, sedative/hypnotic, and anxiolytic (Syvälahti and Hietala, 2001). They are used for treating a range of psychiatric and medical disorders, and are widely used in the treatment of psychological distress related to chronic medical or psychiatric conditions or substance use disorders (Woods et al., 1992).

The medical indications for BZs include cerebral seizures, epilepsy, central spasticity, muscle tension, and various applications in anesthesiology and emergency medicine (Möller, 1999). In psychiatry, established indications for BZs comprise sleep disorders (Holbrook et al., 2000; Roth et al., 2001; Smith et al., 2002), alcohol withdrawal syndrome (Williams and McBride, 1998a; Holbrook et al., 1999), and most anxiety disorders (Argyropoulos and Nutt, 1999; Leinonen et al., 2000). In treatment of sleep disorders, BZs are mostly recommended for short-term use (Partinen and Appelberg, 2002). While they are the primary treatment for alcohol withdrawal syndrome, no evidence exists of their benefit in treating alcohol dependence (Nutt et al., 1989; Malcolm, 2003). In the first weeks of treating depression, BZs combined with antidepressants may be more effective than antidepressants alone (Furukawa et al., 2001). BZs are also useful in the management of psychotic agitation (Wolkowitz and Pickar, 1991) and catatonia (Hawkins et al., 1995).

Table 1. Metabolism and half-lives of benzodiazepines and zopiclone

Benzodiazepine	Major active metabolites[a]	Half-lives (h)[a]	Normal daily dosage (mg)[b]	Time to peak plasma level (h)[b]	Main clinical use
Short-acting benzodiazepines					
Alprazolam	None	9-30	0.25-4	1	Anxiety
Lorazepam	None	8-25	0.5-4	2	Anxiety
Midazolam	None	1-5	7.5-15	0.3-1	Insomnia
Oxazepam	None	5-15	10-120	1-5	Anxiety, insomnia
Temazepam		3-38	10-20	< 1	Insomnia
	Oxazepam	5-15			
Triazolam	None	1-4	0.125-0.25	1-2	Insomnia
Zopiclone[c]		3-6	5-15	0.5-1.5	Insomnia
Intermediate-acting benzodiazepines					
Clonazepam	None	10-50	0.5-4	3-12	Epilepsy, anxiety
Long-acting benzodiazepines					
Chlordiazepoxide		5-30	5-100	1-2	Anxiety
	Nordiazepam	50-99			
	Oxazepam	5-15			
Clorazepate[d]		2	5-30		Anxiety
	Nordiazepam	50-99			
	Oxazepam	5-15			
Diazepam		20-50	2-30	0.25-1.5	Anxiety, epilepsy, muscle spasm
	Nordiazepam	50-99			
	Oxazepam	5-15			

[a]United Nations, 1997
[b]Koponen, 2002
[c]Data on zopiclone from Syvälahti and Hietala, 2001
[d]Data on clorazepate from Tacke and Mattila, 1994. Clorazepate is a pro-drug metabolized to nordiazepam.

Mainly because of long-term safety issues, BZs are increasingly becoming a second choice medication in treatment of anxiety disorders such as panic disorder (Ballenger et al., 1998; Bennett et al., 1998; the Finnish Medical Society Duodecim and the Finnish Academy 2000; Kasper and Resinger, 2001), generalized anxiety disorder (Mahe and Balogh, 2000; Gorman, 2002), post-traumatic stress disorder (Van Etten and Taylor, 1998; Turner *1999*), and social anxiety disorder (Brunello et al., 2000; Pollack, 2001; van Ameringen and Mancini 2001). They are not regarded as useful in obsessive-compulsive disorder (Greist and Jefferson, 1998). However, in clinical practice, they are still more widely prescribed for treatment of anxiety disorders than antidepressants (Stahl, 2002).

Adverse effects of BZs include drowsiness, dizziness, ataxia, mild cognitive deficits, anterograde amnesia, and, rarely, allergic reactions (Sadock and Sadock, 2003a). Paradoxical reactions may occur, manifesting as anger or impulsive behavior (Hall and Zisook, 1981; Cole and Kando, 1993). An overdose can cause confusion, slurred speech, drowsiness, ataxia, and respiratory depression (Sadock and Sadock, 2003a). Alcohol and other sedative-hypnotic compounds interact with BZs, augmenting their effects. The combinations can result in marked drowsiness, disinhibition, or respiratory depression (Sadock and Sadock, 2003a). Some findings suggest that as needed (p.r.n.) BZ users may be more avoidant than regular BZ users and show fewer reductions in sensitivity to anxiety (i.e. fear of body sensations) (Westra and Stewart, 2002). Memory impairment observed during BZ treatment may be transient

(Kiliç et al., 1999), but the findings of one cohort study suggest that BZs might be a risk factor in dementia (Lagnaoui et al., 2002).

Long-term BZ therapy has also been reported to not necessarily produce neuropsychologic deficits in patients with diagnosed anxiety disorders (Gladsjo et al., 2001). There is no evidence that BZs inhibit bereavement (Warner et al., 2001).

Withdrawal symptoms may occur when BZs are discontinued. These present as sedative-hypnotic type symptoms (Michelini et al., 1996) and include autonomic hyperactivity (e.g. sweating, tachycardia), increased hand tremor, insomnia, nausea or vomiting, transient visual, tactile, or auditory hallucinations or illusions, psychomotor agitation, and anxiety. With high doses, delirium, cerebral seizures, and psychotic reactions are possible (Sadock and Sadock, 2003a). The onset of withdrawal symptoms usually occurs 2-3 days after cessation of use, but with long-acting derivatives the latency may be 5-6 days (Sadock and Sadock, 2003a).

2.3. Definition of benzodiazepine abuse and dependence

Substance dependence and abuse have been measured according to several classification systems used in clinical, research, or statistical settings. The most widely used classifications are the International Classification of Diseases (ICD), developed by the World Health Organization (WHO), and the Diagnostic and Statistical Manual of Mental Disorders (DSM), developed by the American Psychiatric Association (APA). Successive versions of DSM have been coordinated with ICD versions since 1952, when DSM-I was published (American Psychiatric Association, 1994). The primary function for the early versions of ICD was the need to collect statistical information, whereas DSM focused on clinical utility. DSM-III introduced for the first time a descriptive approach that attempts to be neutral with respect to theories of etiology.

The three most recent systems, DSM-III-R (American Psychiatric Association, 1987) (see Table 2), DSM-IV (American Psychiatric Association, 1994), and ICD-10 (World Health Organization, 1992) have a common theoretical basis for the concept of substance dependence. They reflect the concept of "alcohol dependence syndrome" which was described in 1976 by Edwards and Gross. In each system, the definitions of dependence and abuse are similar for all addictive substances included, with minor modifications. They all include criteria for withdrawal, use of the substance to relieve withdrawal, tolerance, compulsion to use, salience of using the substance, and relapsing repeatedly to using the substance. In the older DSM-III classification (American Psychiatric Association, 1980), dependence is defined differently; a pattern of pathological use or impairment in social or occupational functioning is usually present, but in some cases, the manifestations of the disorder are limited to physiological dependence. A central feature in the DSM-III version is that either tolerance or withdrawal is required, while in ICD-10 and in the later DSM editions the criteria of dependence can be met without having physiological dependence.

Definitions of abuse differ more between these classification systems. In DSM-III, the abuse criterion (i.e. a pattern of pathological use for at least one month that causes impairment in social or occupational functioning) usually also pertains to dependence. By contrast, both DSM-III-R and DSM-IV require that the criteria of substance dependence have never been met, and that adverse consequences of repeated use be present. DSM-III-R and DSM-IV are fairly similar, although in DSM-IV the criteria are broader. ICD-10 does not use the term "abuse", but includes a category of harmful use, which is conceptually different and is limited to use that causes impairment of physical or mental health.

Table 2. DSM-III-R diagnostic criteria for psychoactive substance abuse and dependence

Psychoactive substance abuse
A. A maladaptive pattern of psychoactive substance use indicated by at least one of the following:
(1) Continued use despite knowledge of having a persistent or recurrent social, occupational, psychological, or physical problem that is caused or exacerbated by use of the psychoactive substance;
(2) Recurrent use in situations in which use is physically hazardous (e.g. driving while intoxicated)
B. Some symptoms of the disturbance have persisted for at least 1 month, or have occurred repeatedly over a longer period of time
C. Never met the criteria for psychoactive substance dependence on this substance

Psychoactive substance dependence
A. At least three of the following:
(1) Substance often taken in larger amounts or over a longer period than the person intended
(2) Persistent desire or one or more unsuccessful efforts to cut down or control substance use
(3) A great deal of time spent in activities necessary to get the substance, taking the substance, or recovering from its effects
(4) Frequent intoxication or withdrawal when expected to fulfill major role obligations at work, school, or home, or when substance use is physically hazardous
(5) Important social, occupational, or recreational activities given up or greatly reduced because of substance use
(6) Continued use despite knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of the substance
(7) Marked tolerance: need for markedly increased amounts of the substance in order to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount
(8) Characteristic withdrawal symptoms
(9) Substance often taken to relieve or avoid withdrawal symptoms
B. Some symptoms of the disturbance have persisted for at least 1 month, or have occurred repeatedly over a longer period of time

According to a DSM-IV field trial, the dependence criteria for sedatives in the DSM-III, DSM-III-R, DSM-IV, and ICD-10 are likely to lead to highly similar proportions of diagnoses (Cottler et al., 1998). In that trial, DSM-III-R was the most inclusive (33% of the sample diagnosed with dependence), while DSM-IV and ICD-10 were the most conservative (27% diagnosed). However, differences between the diagnostic systems were small. Abuse and harmful use diagnoses, by contrast, varied considerably between the diagnostic sets. DSM-IV scored the same proportion of abusers as DSM-III-R (23%), but considerably more than DSM-III (3%). ICD-10 harmful use was the most inclusive (27%).

Many of the substance dependence and abuse terms are used for a variety of meanings in medical literature, which has lead to overlapping and confusion of terms. The word "dependence" can refer to a behavioral syndrome or to physiological dependence (Jaffe, 1995). Previously, the term "addiction" referred to physiological dependence, implying recreational use, and "habituation" referred to psychological dependence. In 1964, a WHO expert committee recommended the substitution of the term "drug dependence" for both (Kleber, 1990). The word "abuse" also has a dual use; it is used to mean 1) a behavioral syndrome and 2) any use of an illicit substance or any nonprescribed use of a licit drug, or harmful use of legally available substances such as alcohol (Jaffe, 1995).

2.4. Epidemiology of benzodiazepine use

Benzodiazepine use and long-term use. According to national surveys, the prevalence of BZ use in the prior month has varied between 5% and 8% in the countries studied (Woods et al., 1992). In the United States, 8.3% of the adult population had used anxiolytics during the past year in 1990, and 25% had used them daily for at least a year (Woods et al., 1992). A strong tendency towards continued use has been observed. In a Swedish eight-year follow-up of a cohort of BZ users in a community with a general population of about 20,000, nearly 70% continued use during the first follow-up year, and 56% continued to use BZs during the second year of follow-up. After the fourth year, about 90% of these users continued use every follow-up year irrespective of individual characteristics. As a result, exactly one-third of the cohort continued using BZs throughout the eight-year observation period (Isacson et al., 1992).

In Finland, the Social Insurance Institution (Kela) and the National Research and Development Center for Welfare and Health (Stakes) have conducted surveys, in which approximately 6% of the population has been estimated to use BZs annually (Klaukka, 1998). On a defined date in 1995/1996, 2.6% of the population used anxiolytics and 2.8% used hypnotics. Of the subjects using anxiolytics, 44% used them regularly on a long-term basis (Klaukka, 1999). Women used BZs 1.4 times as often as men (Klaukka, 1998). According to the registry data of Kela, of those who used BZs in 1995, 69% continued to use them in 1996 and 56% in 1997 (Klaukka, 1999). The sale of anxiolytics has increased steadily during the past decade, and is now the highest of the Nordic countries. In 2001, the sales reached 30.99 defined daily doses (DDD) per 1000 inhabitants daily (National Agency for Medicines and Social Insurance Institution, 2002).

Unsupervised benzodiazepine use. In the United States, the rate of recreational use of BZs in the general population is substantially lower than that of alcohol or marijuana, and is also lower than that of cocaine. According to population surveys, in 1993, 9.5% of the general population had used tranquillizers nonmedically during the lifetime and 0.5% during the past month (Cohen et al., 1996). In contrast to the general population, a substantial proportion of illicit drug users also use BZs (Woods et al., 1992). In studies on subjects with alcohol use disorders registering for assessment or treatment, 33-40% were recent users of BZs, and about half of them could be considered to use BZs nonmedically during their lifetime (Busto et al., 1993). However, it has been suggested that the high rate of BZ use in subjects with alcohol problems reflects the frequency of anxiety disorders among this population (Ciraulo et al., 1988).

In Finland, the most recent data on the prevalence of drug use in the general population come from a population survey conducted in 2000 (Hakkarainen and Metso, 2001). According to this survey, 4.5% of adults (5.6% of men and 3.4% of women) had used anxiolytics or hypnotics for intoxication purposes during the lifetime, 1.5% during the past year, and 0.6% during the past month. Use of medications (largely BZs) as intoxicants is a considerable problem in Finland among drug abusers. The 1999 census of intoxicant-related cases in health and social services showed that 22% of all of their clients engaged in use of medications as intoxicants (Nuorvala et al., 2000).

Benzodiazepine dependence. In the Epidemiological Catchment Area (ECA) study, using the DSM-III classification, the lifetime prevalence of sedative-tranquillizer use disorders was

estimated to be 1.2% (Regier et al., 1990). The diagnoses of abuse and dependence were reported combined, and the category of sedatives included some other medications (e.g. barbiturates) in addition to BZs (Woods et al., 1992). Hence, the actual lifetime BZ dependence was somewhat lower. In an epidemiologic study in Germany (Munich Follow-up Study), the lifetime prevalence of drug abuse/dependence (DSM-III) was 1.79% (Wittchen et al., 1988), and all were women with BZ abuse/dependence (Wittchen and Essau, 1993). The National Comorbidity Survey (NCS) found lifetime dependence upon anxiolytic, sedative, or hypnotic drugs to be 1.2% using DSM-III-R criteria (Anthony et al., 1994). In a recent survey using ICD-10 criteria, the estimated 12-month prevalence of BZ dependence in an Australian population was 0.4% (Hall et al., 1999).

In psychiatric inpatient populations, three large surveys were conducted in Germany between 1980 and 1985 and in Austria between 1978 and 1981 using ICD-9 criteria, which comprised psychological and/or physiological dependence, and DSM-III criteria, which required signs of physiological dependence (Fleischhacker et al., 1986; Schmidt et al., 1989; Wolf, et al., 1989). In these studies, 0.3% to 2% of patients were dependent on BZs alone, and an additional 0.7% to 1.2% were dependent on BZs in combination with other substances.

BZ dependence is commonly detected in subjects with opioid (Rooney et al., 1999; Ross and Darke, 2000) or alcohol dependence, often combined with other substance use disorders (Ross, 1993; Kan et al., 2001). In the Netherlands, the prevalence of BZ dependence was investigated in outpatient addiction centers; using DSM-III-R criteria, 59% of patients were diagnosed with past year BZ dependence and 72% with lifetime dependence. The prevalences were significantly higher in methadone users than nonusers (Kan et al., 2001).

No surveys have been conducted on the prevalence of BZ dependence in Finland. Because the rate of long-term use in Finland equals that in other countries, dependence is also assumed to exist at the same levels as elsewhere (Klaukka, 1998). Among psychiatric referrals in general hospitals in Finland, 30% of women and 13% of men in the age group 35 to 50 years were diagnosed as having ICD-10 sedative or hypnotic use disorders (dependence or harmful use), and alcohol use disorders co-occurred in 22% of females and in 81% of males (Alaja et al., 1997).

Psychiatric disorders co-occurring with benzodiazepine dependence. The research on comorbidity of BZ dependence is not extensive. According to the ECA study (Regier et al., 1990), 74.7% of subjects with sedative-tranquillizer abuse or dependence had other lifetime psychiatric diagnoses: the prevalences were schizophrenia 8.0%, any affective disorder 36.4%, any anxiety disorder 42.9%, antisocial personality 30.3%, and alcohol abuse or dependence 71.3%.

The mechanisms underlying association of substance use disorders with other psychiatric disorders are not well known. There may be causal factors or a shared etiology, and multiple mechanisms of comorbidity are likely (Marshall, 1997; Kushner et al., 2000; Swendsen and Merikangas, 2000; Trull et al., 2000).

In clinical populations, the amount of other co-occurring psychiatric diagnoses varies depending on the setting and selection of cases. Individuals in treatment are more likely to have multiple disorders than cases in the general population (Berkson 1946). In a study conducted in a BZ dependence unit, patients with DSM-III-R BZ dependence were assessed for one-month psychiatric comorbidity, and for personality disorders only one diagnosis was assessed (Martínez-Cano et al., 1999). In that study, all patients received comorbid diagnoses. The prevalences were as follows: anxiety disorders 31% (most frequently panic disorders

with/without agoraphobia, followed by generalized anxiety disorder), affective disorders (mostly dysthymia) 20%, sleep disorders 35%, substance use/withdrawal disorders (mostly alcohol) 20%, somatoform disorders 13%, and psychotic disorders 3%. Personality disorders were diagnosed in 53% of the patients: cluster A (schizoid) 1%, cluster B (histrionic, borderline, antisocial, narcissistic) 17%, and cluster C (obsessive-compulsive, dependent, avoidant, not specified) 31%.

Two studies have been performed, in which patients with BZ dependence admitted to addiction treatment settings were assessed. In the first study, a total of 45% of patients were at discharge diagnosed with psychiatric diagnoses (DSM-III-R), excluding substance use disorders (current depressive disorders 18%, adjustment disorders 14%, anxiety disorders 4%), and 92% with other substance abuse diagnoses (Malcolm et al., 1993). In the other study, all patients had at least one additional lifetime DSM-III-R diagnosis (major depression 33%, panic disorder 30%, alcohol abuse/dependence 53%, opioid abuse/dependence 77%), with the current proportions being 13% for depressive disorders, 13% for panic disorder, 3% for alcohol abuse/dependence, and 47% for opioid abuse/dependence. In addition, 20% were diagnosed with current generalized anxiety. Eighty-eight percent had at least one personality disorder (antisocial 42%, avoidant 25%, borderline 17%) (Busto et al., 1996).

According to a study conducted in Canada on patients registering over a one-year period at an addiction treatment facility, the odds of having a current DSM-III psychiatric disorder were highest in those qualifying for a diagnosis of barbiturate/sedative/hypnotic abuse (Ross et al., 1988). In another large study on substance use disordered-treatment populations in the United States, using DSM-III-R criteria, the diagnosis of lifetime depression was most often associated with prescription drug use disorder among all substance use disorders (62.2% for males and 76% for females) (Miller et al., 1996).

Personality disorders of subjects with substance dependencies (DSM-III-R) were assessed in a study where personality disorder diagnoses were examined by drug-of-choice category. In subjects with sedatives as a drug of choice, 46% were diagnosed with a personality disorder (borderline, avoidant, dependent, and obsessive-compulsive) (Thomas et al., 1999). Similar rates of personality disorders were also detected in other drug-of-choice categories (alcohol, cocaine, opiates, polysubstance, and cannabis). However, some of the cell sizes in the study were small.

2.5. Mechanisms of benzodiazepine dependence

GABA/Benzodiazepine receptors. Gamma-aminobutyric acid (GABA) is the major fast-acting inhibitory transmitter in the central nervous system (CNS). GABA is synthesized from L-glutamate by the enzyme glutamic acid decarboxylase and metabolized mainly by the enzyme GABA transaminase into succinic semialdehyde. BZs act by facilitating GABA-mediated transmission in the CNS (Bateson, 2002). In the presence of GABA, they promote the opening of anion-selective ion channels, causing influx of primarily chloride into neurons, hyperpolarization, and inhibition of cell firing in the mature nervous system. Their binding site is at the $GABA_A$ receptor, which also possesses binding sites for other compounds such as barbiturates, neurosteroids, alcohol, and channel blockers. Structurally, the $GABA_A$ receptor is a pentameric complex that can be formed from several classes of subunits, which additionally have different isoforms. Most of the $GABA_A$ receptors comprise α, β, and γ subunits.

Animal research suggests various mechanisms for development of BZ tolerance and dependence and manifestations of BZ withdrawal (Podhorna, 2002). Changes in the $GABA_A$/BZ receptor function, changes in the serotonin, noradrenaline, cholecystokinin, glutamate, and acetylcholine neurotransmitter systems, altered brain metabolism, as well as altered function of calcium channels have all been suggested as underlying mechanisms. Research on the theory of downregulation of receptor number after chronic exposure to BZs has given mixed results. Newer theories include uncoupling of the allosteric linkage between the GABA and BZ sites, changes in receptor subunit turnover, and altered receptor gene expression. Bateson (2002) has hypothesized that tolerance to the effects of chronic BZ intake is associated with the expression of aberrant $GABA_A$ receptors as a consequence of changes in the expression of $GABA_A$ receptor genes. Withdrawal symptoms manifest when these aberrant receptors have to function in the absence of the drug (Bateson, 2002). It should be noted that animal models of BZ dependence have not been developed for any of the complex human systems. Moreover, dependence on multiple drugs can result in a number of additional adaptational mechanisms never tested in experimental work.

Neurobiological mechanisms. Most addictive drugs are known to act primarily on the brain mesocorticolimbic dopamine system (Kelley and Berridge, 2002). This system connects the ventral tegmental area through the midbrain to the limbic cortex and nucleus accumbens, and amygdala, prefrontal cortex, and other forebrain regions. Evolutionarily, this system evolved to respond to natural rewards, such as food and sex, which were important for survival and reproduction.

No consensus exists about the exact nature of the psychological reward function mediated by the mesocorticolimbic system in addiction. Two factors that modulate behavior - reinforcement and neuroadaptation - are supposed to contribute to the addictive process (Roberts and Koob, 1997). The theories of positive and negative reinforcement assume that the mesocorticolimbic system chiefly mediates the pleasure of addictive drugs and/or anhedonia during withdrawal (Kelley and Berridge, 2002). Reward-learning theories assume sensitized or altered cellular mechanisms of associative stimulus-response learning. Both primary stimuli (e.g. food) and conditioned stimuli (e.g. a specific environment) activate dopamine neurons, and as a result, the conditioned stimuli alone can evoke the conditioned response. The motivational effects of drugs are also conditioned through associative learning. According to this hypothesis, drug-taking habits are a consequence of conditioned reward predictions (Di Chiara, 1995, 1999). The incentive-sensitization or sensitization of "wanting" theory assumes that repeated exposure to drugs induces neuronal adaptation, which is expressed as hypersensitivity to the drugs and the stimuli associated with them. By associative learning, the drugs and stimuli are labeled as excessively desirable (incentive salience). This sensitization of neural systems mediating motivation or "wanting" may occur independently of changes in the systems mediating feelings of pleasure ("liking") induced by the drug (Robinson and Berridge, 1993; Berridge and Robinson, 1998).

Reward-related behavior is also assumed to emerge from the activity in other brain structures that interact with the ventral tegmental area and basal forebrain utilizing GABA, serotonin, noradrenaline, cholecystokinin, glutamate, and acetylcholine as neurotransmitters (Berridge and Robinson, 1998; Markou et al., 1998; Koob and LeMoal, 2001; Kelley and Berridge, 2002; Podhorna, 2002). Corticotropin-releasing factor, neuropeptide Y, and somatostatin neurotransmission have also been hypothesized to have roles in reward and motivational processes (Markou et al., 1998).

According to animal studies, the addictive effects of BZs seem to be mediated through circuits other than the mesocorticolimbic dopamine system, as BZs do not increase its dopamine neurotransmission (DiChiara et al., 1993; Robinson and Berridge, 1993). BZ agonists have been found to induce feeding in animals in many situations and to enhance hedonic affective reaction to sweet and other tastes (Berridge, 1996). This has been assumed to be due to activation of processes relevant to normal appetite, rather than to other known BZ effects. Studies in rats indicate that the effects are caused by circuits in the brainstem (Berridge and Robinson, 1998). Because BZ agonist (diazepam) can enhance hedonistic taste reactivity even in rats that have 98% to 99% depletion of dopamine, the "wanting" and "liking" components of reward have been hypothesized to be mediated by separate neural substrates (Berridge and Robinson, 1998). Besides the opioid system, other systems such as BZ/GABA neurotransmitter systems in the brainstem and the ventral pallidal systems that mediate feeding appear to be related to "liking" (Berridge, 1996).

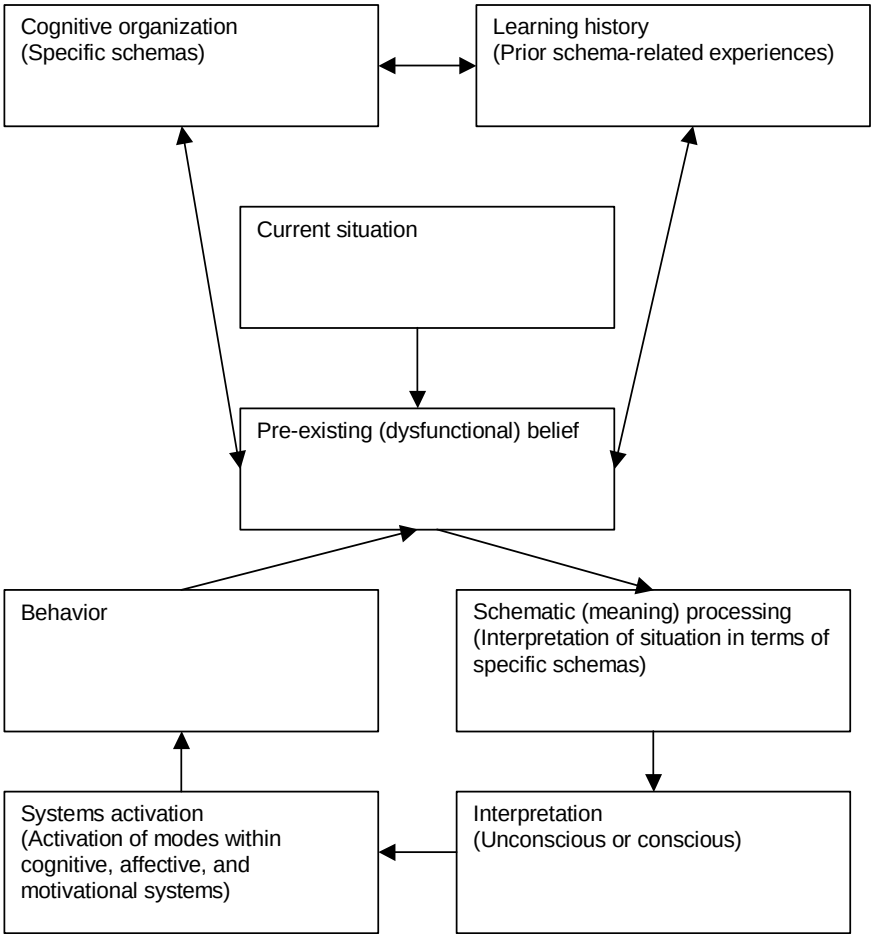
Cognitive theories. The term cognition refers to the mental processes involved in knowing, learning, and understanding (Toskala, 2001). Earlier, cognitive processes were seen as being the opposite of emotions. The contemporary view is that emotions and cognitions cannot be entirely separated and that emotions constitute an essential component in cognitions. Cognitive approaches posit that initiation and maintenance of psychoactive substance use arises from the operation of information-processing systems. Two types of cognitive theories exist; cognitive-behavioral models emphasize such constructions as expectancies, attributions, imitation, and self-efficacy in the control of behavior, whereas the cognitive science paradigm focuses on information processing, cognitive architectures, memory, and decision-making (Tiffany, 1999).

Cognitive-behavioral (i.e. social learning) models. Bandura (1969) introduced the theory of social learning, emphasizing the importance of vicarious learning (modeling) and the cognitive mediation of behavior regulation. The first major cognitive-behavioral approach to substance abuse, developed by Marlatt and Gordon (1985), was the social learning theory of relapse and relapse prevention. Its central feature is that in a given "high-risk situation" the likelihood of relapse to drug use will depend on the subject's expectations. Beck et al. (1993) suggested that dysfunctional beliefs about the perceived need for a drug generate expectations that elicit the craving. They extended Marlatt's theory by defining four types of craving: (1) craving in response to withdrawal symptoms; (2) response to lack of pleasure (e.g. feelings of boredom, negative thoughts); (3) "conditioned" response to drug cues (linking of originally neutral stimuli to drug-induced reward through a process of classical conditioning); (4) response to hedonic desires (e.g. the habit of combining drugs and sex). By the term cue is meant antecedents of drug-taking behavior; affects, thoughts, events, environments, or anything that one has learned to associate with that behavior. Figure 1 presents Beck's cognitive model of information processing. The theory of social learning has been widely adapted as a basis for various cognitive-behavioral treatments (Wilson, 1987; Miller et al., 1995; Liese and Najavits, 1997; Tiffany, 1999; Drummond, 2001; Kadden, 2001).

Cognitive science models. Cognitive science theories focus on information processing, cognitive architectures, memory, and decision-making (Tiffany, 1999). The cognitive processing model differs from other cognitive models in that it posits that drug use is essentially an automatic process like driving a car, and is therefore usually carried out without

conscious awareness. Thus, craving will not occur unless plans for drug-taking are impeded. When access to the drug is hindered, a nonautomatic, effortful cognitive process is elicited, conceptualized in the model as "constellations of verbal, somatovisceral, and behavioral responses supported by nonautomatic cognitive processes" (Tiffany and Conklin, 2000). This theory requires further testing in clinical populations (Drummond, 2001).

Figure 1. Cognitive model of information processing by Ahlford and Beck (Kuusinen, 2001)



2.6. Factors associated with benzodiazepine dependence

Reinforcing effects of benzodiazepines. Drug reinforcement refers to a process where a drug increases the likelihood of behavior that produces it. In animal studies, rapidly eliminated BZs midazolam and triazolam maintain higher rates of self-administration than more slowly eliminated BZs (Griffiths and Weerts, 1997). Data also suggest that BZ administration

facilitates ethanol consumption and the development of ethanol dependence in rats (Martijena et al., 2001).

Laboratory research in humans indicates that the reinforcing effects of BZs are intermediate relative to other sedative compounds (Griffiths and Weerts, 1997). BZs are less efficacious reinforcers than, for instance, pentobarbital and more efficacious reinforcers than sedative compounds believed to have low abuse liability, such as imipramine or buspirone. Higher BZ doses are usually associated with greater reinforcing effects than lower doses. There seems to be contextual determinants of reinforcing effects; the reinforcing effects of a BZ can be modulated in the context of different behavioral tasks following drug ingestion. In addition, BZ self-administration is reduced when the operant work required to obtain the drug increases or when the minimum interval imposed between ingestions increases. Further, the speed of onset of drug effects partly determines the reinforcing effects. In studies of different release rates of the same compounds, the immediate-releasing formulations generally produce greater increases in positive subjective effects. Moreover, compounds with rapid onset of effects (e.g. diazepam) produce greater positive effects than those with slower onsets of effects (e.g. oxazepam).

Clinical data indicate that the clinical potency of a BZ derivative predicts its dependence potential (Tyrer, 1993). Clinical potency is indicated by recommended daily dosages (Feldman et al., 1997a). Patients who abuse substances seem to prefer BZs like diazepam and alprazolam to others with slower onset of effects, based on their reinforcing properties but also their availability on the street (Cole and Chiarello, 1990; Malcolm et al., 1993; Busto et al., 1996).

Patient factors. BZs are almost invariably reinforcing in subjects with histories of drug abuse (Griffiths and Weerts, 1997). They have also been found to function as reinforcers in subjects with histories of moderate but not light social alcohol drinking. Studies in other populations have produced mixed results. BZs have been demonstrated to function as reinforcers in some anxious subjects and in persons suffering from insomnia. The role of physical dependence in BZ reinforcement has been seldom studied, and these results have failed to demonstrate drug reinforcement consistently. One clinical study examining the relationship between prior BZ use and withdrawal difficulties following brief BZ therapy found no association (Rickels and Freeman, 2000).

Patients who have a history of alcohol abuse or dependence are usually excluded from clinical trials using BZs. In one study in which 35% of subjects had a prior history of alcohol abuse or dependence, the subjects showed no signs of dose escalation over time (Romach et al., 1995). In another prospective study involving patients taking BZs at the time of entry, at a 12-month follow-up, no clinically significant differences were present between patients with a history of alcohol abuse or dependence and other subjects (Mueller et al., 1996). Consequently, it has been suggested that a history of substance abuse may not be a major risk factor for future BZ abuse or dependence (Ciraulo et al., 1988; Ciraulo and Nace, 2000; Posternak and Mueller, 2001). However, this construct stems more from a lack of evidence against the dangerousness of BZ use for this patient group than from evidence for BZ safety.

Clinical evidence indicates that subjects with personality disorders may have a higher risk of developing BZ abuse or dependence (Ashton, 1989; Tyrer, 1989; American Psychiatric Association, 1990). This assumption is supported by the finding that patients with a personality disorder experience withdrawal reactions more frequently than those without (Tyrer and Owen, 1983; Schweizer et al., 1990; Murphy and Tyrer, 1991). One recent study

emphasized the importance of personality characteristics for early dropout of taper before patients reached more than relatively mild withdrawal symptoms, explaining this by the sensitivity of these individuals to internal cues (Schweizer et al., 1998). Laboratory studies on reinforcing effects of BZs in subjects with personality disorders are, however, lacking.

Dose and duration of benzodiazepine use. Schmauss et al. (1987) studied patients who had been taking different therapeutic doses of BZs and found no overall differences in the intensity of withdrawal. However, two patients using larger doses exhibited psychotic reactions. Rickels et al. (1988, 1990) and Schweizer at al. (1998) reported that patients taking larger daily doses of BZs were less successful in discontinuing BZ use. Higher doses of BZ are thought to be more likely to produce dependence (Rickels et al., 1999).

Case reports and studies of short-term administration have indicated that discontinuance symptoms may occur after less than four weeks of BZ use (Noyes et al., 1988; American Psychiatric Association, 1990; Schweizer and Rickels, 1998), and several studies suggest that 4-6 weeks of regular BZ administration in therapeutic doses produces symptoms of withdrawal in some patients (American Psychiatric Association, 1990). Four to eight months appears to be the critical time period for the development of physical dependence on BZ anxiolytics (Noyes et al., 1988; American Psychiatric Association, 1990). BZ discontinuation studies have led to the conclusion that nearly half of long-term users who have taken BZs for an average of three years are at risk for withdrawal effects (Noyes et al., 1988). However, it is not quite clear how well the study subjects represented all long-term BZ users in the general population (Woods et al., 1992). Rebound insomnia has been reported after use of BZ hypnotics for only 1 or 2 weeks at therapeutic doses (Noyes et al., 1988; American Psychiatric Association, 1990).

Differences between benzodiazepines. The nature of withdrawal symptoms is similar for long and short half-life BZs, but the time of onset varies (American Psychiatric Association, 1990). More severe symptoms and larger dropout rates have been observed when short half-life BZs are abruptly withdrawn as compared with long half-life BZs (Tyrer et al., 1981; Rickels et al., 1990). No significant differences in outcome or withdrawal experience were observed after a gradual four-week discontinuation between subjects taking long half-life (diazepam or clorazepate) and those taking short half-life (lorazepam or alprazolam) BZs (Schweizer et al., 1990). In another study where the effects of gradual withdrawal of lorazepam, diazepam, and bromazepam were compared, no differences were present between the groups in completion of a gradual withdrawal treatment (Murphy and Tyrer, 1991). BZ half-life seems to be more important for abrupt than for gradual medication discontinuation (Woods et al., 1992).

2.7. Research on benzodiazepine discontinuation

Natural outcome of long term-use. In a cohort of subjects with continuous BZ use of more than four years, 10% stopped using them each year during the next four years (Isacson et al., 1992). However, the definition of continuous use in that study covered a wide range of use patterns, from occasional prescriptions to daily use. Two studies have been conducted where prescriptions in general practice were monitored. In the first study, patients who had used BZs regularly for at least six months were randomized into two intervention groups receiving help for reducing BZ use and one age- and sex-matched control group (Cormack et al., 1994).

After a six-month follow-up, 6% of subjects in the control group had received no BZ prescriptions, while the rates for the intervention groups were 13% and 26%. In the other study, the case notes for patients who had used BZs continuously for 12 months or more were reexamined after nine months (Hawley et al., 1994). Seventeen percent of patients had either stopped or reduced their dose to less than 25% of the initial dose. One study followed up long-term BZ users who had been screened for entry into a BZ discontinuation program but had been excluded from the program for medical or administrative (e.g. unable to keep appointments) reasons or at their own request (Rickels et al., 1991). At a three-year follow-up, 14% were BZ-free. No studies exist on the natural outcome of subjects with diagnosed BZ dependence.

Pharmacological treatments. Gradual BZ dose reductions and switching to a long half-life BZ, such as diazepam, have demonstrated efficacy in the management of BZ discontinuation after long-term therapy (Roy-Byrne and Ballenger, 1993; Rickels et al., 1999). Many of the BZ discontinuation trials have used four-week tapering programs, which seem to be too short for most long-term users (Rickels et al., 1999). Recently, it has been suggested that the dose be reduced and the diminished dose be maintained for several months before the final discontinuation step is initiated (Rickels et al., 1999).

Carbamazepine and sodium valproate, which may enhance GABA-ergic function, improved BZ taper success more than placebo in subjects receiving BZ treatment for at least the past year (Schweizer et al., 1991; Rickels et al., 1999). One study evaluated the efficacy of carbamazepine during alprazolam discontinuation in patients with panic disorder and generalized anxiety disorder who had earlier participated in a two-month trial of alprazolam treatment (Klein et al., 1994). Carbamazepine was found to exert no beneficial effect on patients with generalized anxiety disorder, while it appeared to improve outcome in the panic-disordered patients. The authors suggested that panic-disordered patients were more vulnerable to withdrawal.

Negative results are reported for propranolol, 5-hydroxytryptamine-3-receptor antagonist ondansetron, tricyclic antidepressant dothiepin, buspirone, and progesterone in facilitating BZ discontinuation (Rickels et al., 1999). On the other hand, buspirone has been demonstrated to improve BZ discontinuation outcome when treatment was initiated several weeks before beginning BZ withdrawal in patients with generalized anxiety disorder taking lorazepam for three months or less (Delle Chiaie et al., 1995). The antidepressants trazodone and imipramine have shown beneficial results compared with placebo in BZ discontinuation for patients with generalized anxiety disorder, who had been taking BZs at therapeutic doses for the past 12 months (Rickels et al., 1999, 2000). The hypothesized mechanisms are their ability to reduce levels of depression and anxiety as well as produce alterations in monoaminergic neurotransmission related to BZ withdrawal syndrome. However, in clinical studies, these compounds have not decreased withdrawal severity, although they have improved taper success rate. Furthermore, in general practice patients with depression (DSM-III-R) who had used BZs daily for at least three months, addition of the serotonin selective reuptake inhibitor antidepressant paroxetine to gradual BZ withdrawal was no better than placebo (Zitman and Couvée, 2001). In conclusion, no consistent evidence exists for the benefit of adjuvant medications in facilitating gradual BZ discontinuation, although carbamazepine, valproate, and antidepressants may be useful (Rickels et al., 1999).

Psychological treatments. Cognitive-behavioral therapies have proved to be the most effective psychological approach in withdrawing patients from long-term BZ use (Spiegel, 1999). Cognitive-behavioral treatments are broad-spectrum, placing the primary focus not on dependence per se but also on life areas functionally related to substance use. Both cognitive and behavioral techniques are used to produce therapeutic change (Miller et al., 1995; Liese and Najavits, 1997; Kadden, 2001). Although the central themes of the therapies vary, there are several strategies common to most of the approaches. These include monitoring substance use, motivational interviewing, identifying the cognitive-behavioral events leading to substance use, managing cravings, focusing on treatment retention, attending to coexisting psychiatric symptoms, emphasizing harm reduction, enhancing social support, and identifying lifestyle changes and the associated coping skills needed (Liese and Najavits, 1997).

The studies investigating cognitive-behavioral treatment are presented in Table 3. Skinner (1984) examined the efficacy of providing lessons in anxiety management to general practice patients who had used BZs for at least three months. Most of the patients discontinued their BZ medication, but as no control group was used, determining the extent to which the success was due to psychological intervention is not possible. Cormack and Sinnott (1983) carried out a general practice-based study in patients who had taken BZs continuously for at least one year. No significant differences were found between patients who joined a treatment group and those who were advised by letter to cut down their medication. The patients were not, however, randomly allocated to the groups. Onyett and Turpin (1988) found in a general practice long-term user population no significant difference between cognitive-behavioral group treatment and individual appointments with a general practitioner. Fraser et al. (1990) compared behavioral treatment with no treatment and general practitioner help in a long-term user group. At follow-up, no statistical difference was present in the number of prescriptions of BZs for patients receiving either form of professional help. In general practice studies, psychological interventions might not have a great advantage over less intensive approaches in patients who have not experienced difficulties in previous attempts to reduce their medication.

Tyrer et al. (1985) described a cognitive-behavioral approach to BZ reduction in two patients who had failed to withdraw from their medication with other treatment approaches. Higgitt et al. (1987) studied general practice patients taking BZs for at least the past 12 months. Most of these patients had previously tried to stop their medication. They compared a group receiving cognitive-behavioral therapy with subjects receiving a telephone contact with the same schedule and content. However, the sample size was too small to find any significant differences between the groups. Of the entire subject pool, 25% discontinued their medication. Sanchez-Craig et al. (1987) studied patients who had used BZs for at least three months and who reported an inability to discontinue use. They compared a rapid 4- to 5-week drug taper with abrupt cessation in subjects receiving cognitive-behavioral treatment. By the end of treatment, 39% of subjects who received gradual BZ withdrawal and 58% of those receiving placebo alongside cognitive-behavioral treatment became abstinent. Unfortunately, these studies lacked control groups receiving no cognitive-behavioral treatment.

In a study on patients with panic disorder who had received alprazolam or clonazepam for at least six months, most of the subjects receiving cognitive-behavioral treatment (76%) successfully discontinued their medication, while only a minority of those receiving taper alone (25%) discontinued BZs (Otto et al., 1993). In another study on panic disorder patients receiving alprazolam for at least four weeks before inclusion in the study and maintained at a stable dose for a mean duration of 11 weeks before BZ taper, no difference was found between taper only and cognitive-behavioral treatment in the rate of discontinuation (80% and

Table 3. Studies on cognitive-behavioral treatment (CBT) in benzodiazepine discontinuation

Study	Treatments	Subjects	Outcome	Comment
Cormack and Sinnott, 1983	Group treatment lasting 11-13 weeks vs. no psychological treatment	General practice patients; BZ use for at least one year; N=42	5/11 in the treatment group and 12/31 not receiving psychological treatment reduced their medication	No randomization to groups
Skinner, 1984	6 group sessions	General practice patients; BZ use for at least 3 months; N=30	Most withdrew or reduced their medication	No control group
Tyrer et al., 1985	10 sessions of CBT vs. relaxation therapy	Patients with previous failure to withdraw; N=3	The two receiving CBT withdrew completely	Randomization of 3 subjects
Higgitt et al., 1987	20 sessions of group treatment vs. telephone contacts with the same contents	Chronic users with previous attempts to withdraw; BZ use for at least 1 year; N=16	25% withdrew completely	Naturalistic study; the groups were combined in outcome analyses
Sanchez -Craig et al., 1987	Maximum 8 individual sessions of CBT	Chronic users with previous attempts to withdraw; BZ use for at least 3 months; N=42	39% withdrew in the gradual discontinuation group; 58% withdrew in the placebo (abrupt discontinuation) group	Randomization to gradual drug discontinuation and placebo conditions
Onyett and Turpin, 1988	5 group treatment sessions vs. individual appointments with a general practitioner	Chronic users; BZ use for 4 months or longer; N=18	At follow-up, 77% were taking a quarter or less of their original dose; there was no difference between the interventions	Randomized allocation as far as possible, but the group condition was filled first
Fraser et al., 1990	6 sessions of group treatment vs. appointments with a general practitioner vs. no treatment	Chronic users; BZ use for a minimum of 1 year; N=30	At follow-up, fewer prescriptions had been requested by patients in the two groups receiving professional help	Controlled, randomized study
Otto et al., 1993	Taper with 10 group sessions of CBT vs. taper alone	Panic disorder patients; BZ use for 6 months or longer; N=33	76% in the CBT group withdrew; 25% in the taper alone group withdrew	Controlled, randomized study
Spiegel et al., 1994	Taper with 12 individual sessions of CBT vs. taper alone	Panic disorder patients; BZ use for 3 months or longer (drug stabilization and maintenance periods); N=21	90% in the CBT group and 80% in the taper alone group withdrew; at follow-up 90% in the CBT group and 40% in the taper alone group were BZ free	Controlled, randomized study
Elsesser et al., 1996	9 sessions of complaints management training (CMT) vs. anxiety management training (AMT)	Chronic users; BZ use for at least 6 months; N=44	7 subjects in the CMT group and 5 subjects in the AMT group achieved abstinence	Controlled, randomized study; only 9 CMT and 10 AMT subjects who completed the treatment were included in the outcome analyses

90%, respectively), but half of the subjects who discontinued their BZ use without cognitive-behavioral therapy relapsed during the follow-up (Spiegel et al., 1994).

Two different types of cognitive-behavioral therapy were compared in a study on chronic BZ users with at least six months of regular BZ use and at least one prior unsuccessful withdrawal attempt (Elsesser et al., 1996). Complaints management training, which focuses on reported withdrawal symptoms and conveys specific techniques intended to ease them, was found to be superior to anxiety management training. However, no difference was present between the groups at follow-up.

Predictors of outcome. In a study on patients who had entered a multicenter trial of 5-12 months' alprazolam treatment for panic-related disorders, a gradual dosage reduction scale over a four-week period was conducted at the end of the long-term treatment. Marked differences (21% to 95%) were found between the proportions of patients discontinuing alprazolam treatment at different study sites. The authors concluded that physician attitudes towards discontinuation played a role in determining the ability of patients to discontinue alprazolam therapy (DuPont et al., 1992).

Predictors of successful BZ withdrawal have been examined in the context of discontinuation studies, and therefore the populations have mainly involved subjects with long-term use at therapeutic doses (Woods et al., 1992). The findings of these studies have been partly inconsistent. Younger age (Rickels et al., 1991; Holton et al., 1992) and older age (Rickels et al., 1988; Cormack et al., 1994) and shorter duration of use (Rickels et al., 1988, 1991, 2000) and longer duration of use (Holton et al., 1992) were all found to predict successful BZ discontinuation. No history of previous recreational drug use (Schweizer et al., 1998), lower BZ dose (Rickels et al., 1988, 1990, 2000; Schweizer et al., 1998), and lower level of psychopathology (Rickels et al., 1993, 2000) were associated with favorable BZ discontinuation outcome. Findings of no predictive value of baseline psychiatric variables (Schweizer et al., 1990; Otto et al., 1993; Charney et al., 2000) and BZ dose (Ashton, 1987; Bruce et al., 1995) were contradictory. Passive-dependent personality traits were shown to more constantly predict failure in BZ discontinuation attempts (Rickels et al., 1988, 1990; Holton et al., 1992; Schweizer et al., 1998). The contribution of other personality factors has not been studied.

Research in panic disorder patients has indicated that patients' sense of control over symptoms may improve their response to BZ withdrawal therapy (Başoğlu et al., 1994; Bruce et al., 1999). In the study of Başoğlu et al. (1994), patients who strongly believed it was the tablets that helped them had more severe withdrawal symptoms and deteriorated more often during follow-up. Bruce et al. (1999) followed up panic disorder patients 2-5 years after BZ discontinuation treatment and found that 75% of patients who had received cognitive-behavioral treatment had remained abstinent and maintained their treatment gains, while only 30% of controls were abstinent. Reduction in anxiety sensitivity during treatment predicted follow-up survival. The results support cognitive-behavioral approaches positing that when fear of anxiety sensations is alleviated, there is also a reduction in anxiety symptoms (Otto et al., 1992).

Psychiatric symptom severity after treatment. In a study by Cantopher et al. (1990), patients tended to be less anxious after BZ withdrawal treatment than at baseline, although the trend reached statistical significance in some measurements only. Schweizer et al. (1990) found small but significant improvements in patients five weeks after successful BZ discontinuation

compared with pretaper scores, as measured by the Hamilton Anxiety Rating Scale (HAM-A), the Hamilton Depression Rating Scale (HAM-D), and the Hopkins Symptom Checklist (HSCL) depression subscale. In a study of long-term outcome after BZ withdrawal treatment, subjects who used BZs at the three-year follow-up had more symptoms than BZ-free subjects, assessed with the anxiety and depression factors of the HCSL (Rickels et al., 1991). In another study conducted in generalized anxiety disorder patients, the patients who were BZ-free at a 12-month follow-up after withdrawal treatment reported significantly lower anxiety and depression symptoms, measured with HCSL anxiety and depression factors, than those who continued to take BZs (Rickels et al., 2000). One study reported outcome of subjects with DSM-IV BZ dependence (Charney et al., 2000). During a six-month follow-up the subjects substantially decreased their BZ doses and concurrently their anxiety levels decreased markedly when measured by Symptom Checklist-90 (SCL-90) anxiety subscales. However, no significant differences were detected in HAM-D anxiety subscales. Together these studies indicate that individuals who stop taking long-term therapeutic doses of BZs may attain lower levels of psychiatric symptoms.

3. AIMS OF THE STUDY

This study investigated the effects of a BZ withdrawal treatment program in subjects with complicated dependence (i.e. the majority were taking high BZ dosages or had co-occurring alcohol problems) at outpatient dependence clinics (A-clinics). Further, it examined the predictors of discontinuing BZs and staying BZ-free, and also evaluated the subjects' psychopathology and health-related quality of life. Specific aims of the study were:

1. To evaluate whether gradual BZ taper combined with cognitive-behavioral therapy is more effective than conventional treatment for patients with dependence problems in outpatient clinics (Study I).

2. To describe the comorbidity of subjects with complicated BZ dependence (Study II).

3. To identify which sociodemographic and health characteristics contribute to the outcome of BZ withdrawal treatment in subjects with complicated dependence (Study II) and to evaluate predictors of staying BZ-free (Study III).

4. To assess the long-term outcome of subjects with complicated BZ dependence (Study III).

5. To examine changes in psychopathology, functioning, and quality of life after BZ withdrawal treatment and again after a follow-up period averaging 11 months (Study IV).

4. SUBJECTS AND METHODS

4.1. Diagnoses

The concepts of abuse and dependence were used in this study according to DSM-III-R criteria (Table 2). All of the subjects were diagnosed with BZ dependence. For assessing predictors of BZ cessation and staying BZ-free, some diagnostic metacategories were formed for comorbid axis I and II diagnoses. Personality diagnoses were in analyses treated as cluster A, B, and C disorders. Mood disorders included major depression, dysthymia and bipolar disorder type II. Alcohol and other substance use disorders included both dependence and abuse.

4.2. Subjects

To be eligible for the study, subjects had to meet DSM-III-R criteria for BZ dependence, to be 18-65 years old, and to give consent for participation. Individuals were excluded if they required inpatient treatment for alcohol dependence, as assessed by an AUDIT score of over 30 (Allen et al., 1997), if they had a history of DSM-III-R illicit drug dependence or abuse within the past year, or if they had active medical illnesses or psychoses.

4.3. Treatment settings

A-clinics are public sector outpatient clinics in Finland that provide treatment for alcohol, drug, and other dependencies, offering help for the social, physical, and mental health difficulties connected with these. They provide a flexible range of treatments depending on the situation and case; individual, group, couple, and family therapy is available. Treatments comprise counseling, crisis care, and conversational therapy, often using various forms of brief therapy and solution-oriented methods or, in case of extended treatment, a systemic treatment model. Medical care and outpatient withdrawal treatment are also provided. At the time the study was conducted, A-clinics usually referred illicit drug abusers to a specialized care system.

The sites for the study were chosen from A-clinics in Helsinki. The four A-clinics with the largest staff participated. Each of the clinics was responsible for treating its own district. The staff of one of the clinics was trained to provide the experimental treatment, while the personnel of the other three clinics treated control patients, using their customary treatment strategies. Staff of the clinics consisted of social psychologists, social workers, and nurses.

4.4. Treatments

Experimental treatment. The entire staff of the experimental clinic was trained to provide the experimental treatment. One of the therapists had been working at the clinic for two years and the others from 3 to 4.5 years before the study commenced. All of the therapists were women. Training consisted of lectures and, as a group, studying the manual and related materials (e.g. video) and completing the tasks. The training was carried out during staff meetings in the year prior to the study.

The experimental treatment involved scheduled BZ taper with approximately 1/10 dose reductions weekly after a two-week stabilization period (Ashton, 1994). The duration of the taper thus depended on the pre-taper dose. A slower rate of taper was permitted if the subjects were unable to tolerate the reductions. A clinician monitored the taper. Treatment sessions were given individually once a week, but they were occasionally adjourned for up to three weeks if the subject had other engagements.

Table 4. The experimental program

Session 1. Introduction: -Information on BZ withdrawal treatment -Plan of dose reductions (depending on the subject's initial BZ dose) -Subjects are asked to continue BZ use in their normal pattern and dosage to obtain accurate data on patterns of use -Homework: BZ and alcohol diary
Session 2. Monitoring of BZ and alcohol use: -Review of homework -Monitoring of BZ use continues for 2 weeks -Homework: BZ and alcohol diary
Session 3. The advantages and disadvantages of using BZs: -Review of homework -Advantages and disadvantages of using BZs are discussed to detect personal problems caused by BZ dependence -Stabilization of daily BZ doses, based on the BZ diary -Homework: BZ and alcohol diaries, monitoring of urges to take BZs
Session 4. Personal reasons served by using BZs: -Review of homework -Identification of functions served by BZs in order to develop alternatives -Beginning of BZ dose decreases -Beginning of carrying out other components of the study treatment -Homework: BZ and alcohol diaries, optional homework
Session 5 and following sessions. Coping and skills: -Review of homework -BZ dose decreases according to plan -Subjects are taught to recognize dysfunctional thoughts and attitudes and encouraged to develop alternative coping skills -Educational components of the treatment and teaching a relaxation technique are carried out -Homework: BZ and alcohol diaries, optional homework
After BZ cessation: -Sessions once a week for 1 month, then once a month for 5 months -Focus on counseling and relapse prevention

The experimental program is presented in Table 4. All of the experimental group subjects were expected to participate in the following treatment components: taper plan, BZ diaries, drinking diaries, education on BZ withdrawal by printed material and video film, assessment of BZ functions as a basis for planning alternative ways of coping, and progressive relaxation exercises. In addition, depending on subjects' individual problems, they were given advice on how to deal with high-risk situations, solve problems in general and in couple relationships, handle sleeping problems, and cope with anxiety and depression. This information and related homework assignments were included in a manual that the therapists were instructed to utilize in tailoring the techniques to meet the needs of individual subjects (Table 5). Content of the manual was adapted from Ellis (1977), Higgitt et al. (1987), Sanchez-Craig et al. (1987),

Hammersley and Hamlin (1990), Mason and Norris (1990), and Golombok and Higgitt (1993).

Table 5. Contents of the treatment manual.

1. Information and guidelines for the therapist: -Guidelines for motivational interview -Information on BZs (use and abuse, concomitant alcohol use, pharmacology, effects, adverse effects, withdrawal symptoms) -Insomnia and its treatment (sleep hygiene, relaxation techniques, stimulus control, regular times for going to bed and getting up, changing the appraisals of sleep and background problems) -Anxiety and its treatment (education, physical exercise, relaxation techniques, restructuring dysfunctional thoughts, emotions and attitudes, exposure) -Panic and its treatment (education, restructuring dysfunctional thoughts, methods of decreasing arousal: relaxation, shifting attention to an external focus) -Exposure treatment for avoidance -Depression and its psychological treatment (restructuring dysfunctional thoughts) -Relaxation
2. Forms and questionnaires: Mandatory: -Taper plan -BZ diary -Alcohol diary -Assessment of BZ functions Optional: -Monitoring of drinking urges -Analysis of relapse situations -Dealing with relationship problems -ABC diagram for analyzing dysfunctional thoughts related to behavioral and emotional problems -Problem solving -Planning for change -Coping with high-risk situations -Daily plan -Weekly plan -Sleep diary
3. Material for patients: Mandatory: -Contents of the treatment -BZ dependence and its treatment -BZ dependence (video) Optional printed material: -Self-confidence -Coping with high-risk situations -Coping with stress -Dysfunctional thoughts -Coping with anxiety -Understanding panic

Control treatment. Treatment of control group subjects involved a gradual BZ taper scheduled and managed by a clinician, and discussions with a nurse or therapist. The researchers did not define the rate of the taper or themes of the discussions beforehand. Diaries of BZ doses were used as a basis for dose reductions, but no other agreed-upon techniques were used. Treatments in the three A-clinics differed from each other to some extent. The individual nurses and therapists applied their customary approaches.

At A-clinic 1, the therapists used mainly supportive approaches. Over the course of the study, staff turnover occurred, and the clinic altered its practices; some cognitive approaches were adopted (one of the therapists did cognitive rehearsals and the clinic begun to use educational material similar to that in the experimental clinic), and supportive group treatment was offered to five subjects (total number of subjects 20). Thus, the treatments of the experimental and control groups at this clinic became more similar as they dealt with some common themes. However, treatment was not structured but depended on the approaches of individual therapists.

In A-clinic 2, the treatment orientation was supportive. A doctor planned and monitored a graded BZ reduction, which was carried out by a nurse. In addition, supportive discussions with a therapist were offered. The clinic treated six subjects.

In A-clinic 3, the treatment commenced in a session, in which a doctor, nurse, and therapist together interviewed the patient and planned the treatment. In subsequent sessions, the patients usually met a doctor and a therapist. Some of the subjects also met a nurse, who dealt with daily BZ doses. The approach the therapists used was brief psychotherapy with strength perspective and focused problem-solving techniques. A total of 11 subjects received treatment at this clinic.

4.5. Randomization

Subjects were randomized into two treatment groups by the sealed envelope method. All experimental treatment was offered at one of the clinics, and the individuals who were assigned to the control group received treatment-as-usual at the clinic nearest to their place of residence. Prior to allocation to treatment, other psychotropics were washed out, and BZ use was allowed to stabilize. If the subject met DSM-III-R criteria for major depression, fluoxetine medication was used. Zopiclone was included in the study preparations as a widely used BZ receptor agonist.

4.6. Data collection

Baseline assessment included subjects' medical history as well as histories of drug and alcohol use. The validity of subjects' reports of BZ use was checked by urine and serum tests and documents from treatment settings. Diagnostic assessments were performed with the Structured Clinical Interview for DSM-III-R, Patient Version (SCID-P) (Spitzer and Williams, 1985) and the Structured Clinical Interview for DSM-III-R Personality Disorders (SCID-II) (Spitzer et al., 1990), which were carried out by one of the researchers (H.V.). In patient samples, the overall test-retest reliability of SCID (weighted kappa) has been observed to be 0.61 for current and 0.68 for lifetime diagnoses (Williams et al., 1992). The SCID yields highly reliable diagnoses for most axis I and axis II disorders (Segal et al., 1994). Current mood disorders may be less reliably diagnosed (test-retest reliability 0.42) in subjects with current substance use disorders (Bryant et al., 1992). Diagnosed Axis II disorders seem not to reflect substance-induced conditions, as recovery from substance use disorders does not covary with remission of axis II pathology (Verheul et al., 2000).

A medical examination including serum sampling for BZs, blood count, and gamma-glutamyltransferase (GGT), and urine sampling for BZs and illicit drugs was carried out. BZs were screened in urine samples by using enzyme immunoassay (EMIT) and separately with

thin-layer chromatography for lorazepam, nitrazepam, and clonazepam (Lillsunde and Korte, 1991), and then verified from serum with gas chromatography-mass spectrometry (Lillsunde and Seppälä, 1990).

Assessments included several self-report questionnaires. Alcohol use was measured by the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993), a self-rated form for assessing hazardous and harmful consumption of alcohol during the last year. This test has been derived from an international data set. Its sensitivity and specificity have, however, been similar from country to country (Saunders et al., 1993). The cutoff point for AUDIT is usually set at 8 (range 0-40). The median sensitivity for alcohol dependence or abuse criteria is 0.86 and specificity is 0.89 (Reinert and Allen, 2002). Test-retest reliability and internal consistency are good (Reinert and Allen, 2002).

The Severity of Dependence Scale **(**SDS) (Gossop et al., 1995) assesses psychological components of dependence, with higher scores indicating higher levels of dependence (range 0-15). It has recently been validated for BZ dependence in regular BZ users, with a cutoff point of 7 for dependence (de las Cuevas et al., 2000). The specificity for the Composite International Diagnostic Interview (CIDI) diagnosis of dependence is 92.4% and sensitivity is 97.9%.

The Health-Related Quality of Life (HRQOL) (Revicki et al., 1992) components have been selected from previously developed and validated instruments. It contains measures of energy and fatigue, social behavior, cognitive function, home role function, and general well-being to enable assessment of subjective health status. The scores range from 0 to 100, with higher scores indicating higher functioning and well-being. One of its dimensions, life satisfaction, is measured on a 1-7 scale. The instrument was developed to measure outcomes of treatment of depression, therefore addressing the dimensions of physical functioning, role, social, and cognitive functioning, and general well-being. The intraclass correlation coefficients for test-retest reliability range from 0.74 to 0.97. Its scales are responsive to changes in depression severity (Revicki et al., 1992). Two of its scales (health perceptions and energy/vitality, which feature in the RAND-36 and MOS SF-36 instruments) were validated in Finland after the implementation of this study, and community norms were set (Aalto et al., 1999).

The psychiatric questionnaire Symptom Checklist-90 (SCL-90) (Derogatis et al., 1973) was also recently validated in Finland and community norms were set (Holi et al., 1998). The internal consistency of all of its subscales was good (Cronbach's coefficient alpha ranged from 0.77 to 0.90), and they discriminated well between community and patient samples. Based on principal component analyses, the instrument appears to measure a single global distress factor instead of nine independent symptom subscales (Holi et al., 1998).

The subjects also completed 100-mm visual analogue scales (VAS) for assessing experiences of tension, insomnia, anxiety, and inability to concentrate (Streiner and Norman, 1989). For some of the analyses, the VAS measures were combined into a composite index. The Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman et al., 1992) was rated by three research assistants on a 1-100 scale. Intraclass correlation coefficients between the first rater and the two other raters were 0.91 (95% CI 0.63 to 0.98) and 0.89 (95% CI 0.60 to 0.97).

During treatment, urine BZs were analyzed monthly and serum BZs every three months to confirm subject compliance. End-point assessments were performed two weeks after BZ cessation (Otto et al., 1993) or, in the case of unfinished treatment, after 12 months. These included an interview concerning BZ, alcohol, and illicit drug use, and recent treatments, serum and urine tests, and an AUDIT questionnaire. The same outcome data were obtained

from dropouts as well. Further, documents from treatment settings were obtained and compared with interview data and laboratory tests.

Subjects who had entered the BZ discontinuation study were again assessed 6 and 12 months after termination of the study treatment. This part of the study was conducted as a naturalistic follow-up. The subjects were interviewed about BZ use, use of other medications, use of alcohol and illicit drugs, psychiatric and general medical problems and treatments, affiliations to self-help groups, and demographic data. Documents from the treatment settings were obtained when possible. To assess changes in alcohol use, GGT was measured, and the subjects also completed AUDIT questionnaires at the 12-month interview. BZs were screened in urine samples and verified in serum samples. Subjects returned their self-rated forms after a follow-up period of 4-17 months. Data gathered at the various phases of the study are presented in Table 6.

Benzodiazepine dose equivalents. Dose equivalents used were as follows: diazepam 5 mg, oxazepam 15 mg, alprazolam 0.5 mg, temazepam 5 mg, clonazepam 0.25 mg, lorazepam 1 mg, chlordiazepoxide 10 mg, clorazepate 7.5 mg, midazolam 1.25 mg, triazolam 0.1 mg, and zopiclone 1.875 mg (Goa and Heel, 1991; Kaplan and Sadock, 1993).

Table 6. Data collection during various phases of the study

Treatment phase (max 12 months)													Follow-up phase		
Months	0	1	2	3	4	5	6	7	8	9	10	11	12	+6	+12
Interview	x						x						x	x	x
SCID-P	x														
SCID-II	x														
Medical assessment	x														
Blood count	x						x						x	x	x
GGT	x						x						x	x	x
S-BZ	x			x			x			x			x	x	x
U-BZ	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
U-drugs	x						x						x	x	x
Breath alcohol	x						x						x	x	x
AUDIT	x												x		x
VAS	x	x	x	x	x	x	x	x	x	x	x	x	x		x[a]
SOFAS	x			x			x			x			x		x
SCL-90	x			x			x			x			x		x[a]
HRQOL	x						x						x		x[a]
SDS	x						x						x		x
Treatment documents	x												x		x

[a]Questionnaires obtained after follow-up of 4-17 months.

4.7. Statistical methods

Outcome was assessed immediately after the treatment and after follow-up periods of 6 and 12 months. The principal outcome measure was the proportion of subjects who had successfully completed the taper in each of the treatment groups. BZ discontinuation was defined as no usage of BZs beyond the minimum (minimal usage was defined as no more than 5 mg diazepam or the equivalent for 1 week to ensure that subjects taking occasional minimal doses were not considered failures) for 2 weeks (Otto et al., 1993). Subjects who used BZs, as

measured by the interviews, treatment documents, or urine and serum tests, were defined as users. The other main outcome measures were changes in BZ doses and BZ use categories at the end of the study.

The power to detect a 33% difference in taper outcome between the two treatment groups was calculated to be 80% in a two-tailed test at the 5% level. The main outcome variables were tested using intention-to-treat analyses for all randomized subjects. To clarify whether outcomes were affected by dropouts, additional analyses were performed after excluding subjects who dropped out prior to treatment or for reasons unrelated to treatment (leaving the geographic area, medical problems, other responsibilities such as work or studies).

When assessing follow-up data with repeated measures, likelihood ratio tests for two groups were used to analyze categorical data, and repeated measures analysis of covariance controlled for baseline BZ doses was used to analyze continuous data. Outcome analyses were performed after missing values were replaced with means of the two nearby values or with the last observation carried forward. Additional analyses were performed without replacing missing values. The baseline data of subjects with missing interviews and those with no missing interviews were compared to determine whether possible differences affected the external validity of the study.

To search for predictors of successful BZ discontinuation and staying BZ-free, relevant baseline and treatment data were analyzed with logistic regression. The aim was to find the simplest well-fitting model. Since it was expected that the experimental and control groups would differ significantly in outcome, the treatment condition was included in this analysis. Other variables were chosen based on univariate comparisons. Several possible models were examined. To explore whether the logistic regression result could have been due to covariance of the variables, the potential predictors were compared.

Differences in the change scores between the two study groups were analyzed by the SPSS GLM procedure. To control for baseline differences, analyses of covariance (ANCOVAs) with pre-treatment scores as covariates were conducted for analyzing post-treatment status and with post-treatment scores as covariates for analyzing follow-up status (Vickers and Altman, 2001). The results were verified by multivariate analyses of covariance (MANCOVAs). MANCOVAs were not considered appropriate as the sole analyses due to correlations among outcome variables that could reduce the power of multivariate analyses. To ascertain that imputation of estimates for missing data was not compromising the results, additional ANCOVAs were done without replacing baseline and post-treatment measurements. Changes for the entire subject group were analyzed by paired t-tests. In cases with large variances, the results were ensured by additional analyses using nonparametric Wilcoxon's paired tests. To identify the subjects benefiting most from treatment, the subject sample was divided into three groups based on BZ use during the follow-up. These were 1) no use during the follow-up period; 2) clinically significant decrease (over 50%) of BZ dose by the end of follow-up; 3) 50% or smaller decrease (including those subjects who did not decrease their dose and those who increased their dose). The results were analyzed using ANCOVAs and additional MANCOVAs. Post hoc pairwise comparisons were subjected to Bonferroni adjustment for multiple comparisons. Before the analyses, missing data at baseline (1-4 measures for 5 subjects) were replaced with the first data collected after the beginning of treatment. Likewise, missing data at post-treatment assessment (1-9 measures for 22 subjects) were replaced with the last treatment measurement or with data collected after termination of the treatment. If no such data were available, missing observations were left empty. No follow-up data were substituted; assessments were carried out after a variable follow-up of 4-17 months after the end of treatment (mean follow-up 11 months).

In group comparisons, chi-square and Fisher's exact tests were used for categorical data, and chi-square tests for linear trend (trend test) were used to analyze ordered categories. When the expected frequencies were small, exact *P* values were used. Two-tailed independent sample t-tests or Mann-Whitney *U*-tests were used for continuous data. For comparisons of change scores between groups, nonparametric Kruskall-Wallis tests were performed. In all analyses, results were considered significant at $P<0.05$ with a two-tailed interpretation.

Agreement between interview data and validating information on BZ use (treatment documents, urine and serum tests) was assessed using kappa statistics for categorical data and intraclass correlation coefficients for continuous data.

Data analyses were conducted using the SPSS statistical package, versions 8.0 and 9.0 (SPSS Inc., Chicago, IL, USA).

5. RESULTS

5.1. Formation of study sample

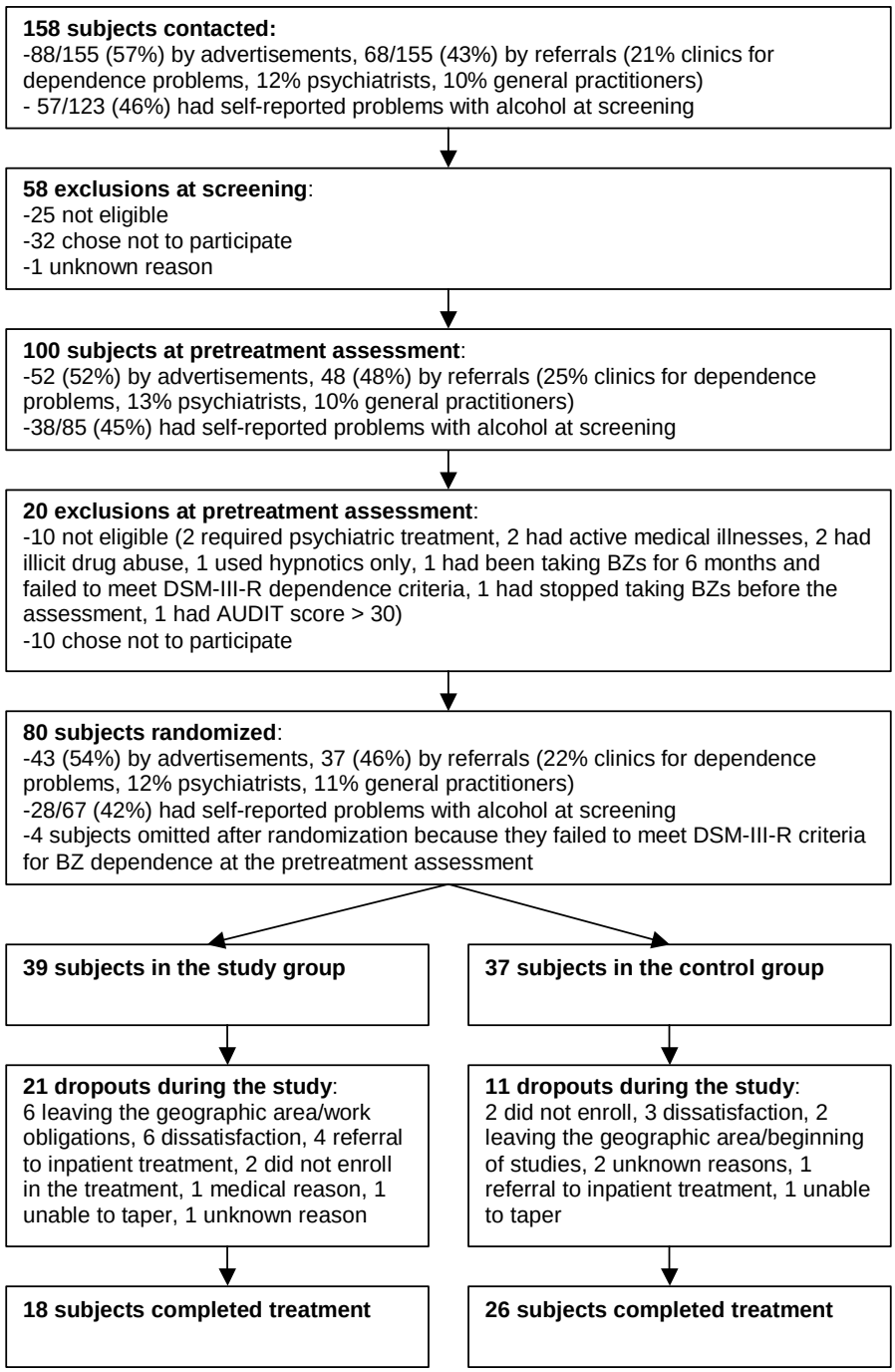
The study was conducted between February 1995 and July 1999. Subjects were recruited over a period of 29 months, until July 1997.

The subject pool comprised patients referred by general practitioners and psychiatrists and volunteers answering advertisements in local newspapers. Altogether 76 subjects participated, with 158 persons initially being contacted and screened by telephone. The 100 subjects who were eligible for the study were interviewed and informed consent was requested. Twenty subjects were excluded from the study during the baseline assessment. The 80 subjects remaining were randomized into the study groups, and four subjects (one in the experimental group, 3 in the control group) were subsequently omitted from the statistical analyses because they failed to meet DSM-III-R criteria for BZ dependence at the baseline interview. The proportion of subjects coming to the study by referral and advertisement and the proportion of subjects with self-reported alcohol-related problems remained unchanged during the screening and assessment procedures preceding the study. Participation in the study procedures is presented in Figure 2.

After randomization, the two treatment groups were comparable with each other in all of the essential variables. The few significant differences between the groups (frequency of lifetime anxiety disorders, frequency of lifetime cluster A personality disorders, and feeling tense as self-rated by VAS) can be seen in Tables 7-9 and 11-13.

In accordance with the study protocol, fluoxetine medication for current major depression or for recurrent depression (3 episodes or more) was started in both treatment groups for 13 subjects (altogether 26 subjects) after the baseline interview.

Figure 2. Flowchart of participation in the study[a]



[a]Information missing fo some subjects

5.2. Characteristics of subjects

Social background. The sociodemographic characteristics of the subjects are presented in Table 7. The mean age ± SD was 40.0 ± 9.6 (range 21-65) years and 55% of the subjects were male. Thirty percent had been educated for no more than 9 years, 54% for more than 9 years (they had either secondary school education without any further studies or nonacademic post-elementary school qualifications), and 16% had university degrees. Nearly half of the subjects were unemployed, and 24% were on pension or students, leaving only 32% in the workforce. There was no difference between the genders in education or employment. About one-third of the subjects were married or cohabiting, one-third were divorced or separated, and one-third never married. Nearly half of the subjects lived alone; 29% had children at home.

Table 7. Pr-etreatment demographic characteristics of subjects by treatment conditions

		Experimental group (N=39)	Control group (N=37)	*P*
Age	Mean (SD)	41.7 (8.9)	38.2 (10.2)	0.11 [a]
Sex, males	N (%)	21 (54)	21 (57)	0.80 [b]
Education	N (%)			0.51 [b]
≤ 9 years		11 (28)	12 (32)	
> 9 years		20 (51)	21 (57)	
University degree		8 (21)	4 (11)	
Occupation (former if on pension or sick leave)	N (%)			0.017[b]
White collar employee		22 (56)	19 (51)	
Blue collar employee		11 (28)	18 (49)	
Others (student, entrepreneur)		6 (15)	0 (0)	
Employment	N (%)			0.33 [b]
Employed		11 (28)	13 (35)	
Unemployed		16 (41)	18 (49)	
On pension, student, at home		12 (31)	6 (16)	
Marital status	N (%)			0.66[b]
Unmarried		13 (33)	11 (30)	
Married or cohabiting		13 (33)	16 (43)	
Divorced or separated		13 (33)	10 (27)	
Housing arrangement	N (%)			0.39[b]
Alone		22 (56)	15 (41)	
With partner		13 (33)	16 (43)	
Other (with parents, with children, with friends)		4 (10)	6 (16)	
Living together with children	N (%)	11 (28)	11 (30)	0.88[b]

[a]t-test.
[b]chi-square test.

Benzodiazepine use history. The data on BZ use of study subjects can be seen in Table 8. The subjects had been using BZs for a variable time, from 8 months to 30 years. The median duration of BZ use was 84 months (i.e. 7 years). The subjects used 10 different BZ preparations and zopiclone. The preparations used were as follows (number of subjects in parentheses): alprazolam (27), oxazepam (25), diazepam (20), zopiclone (17), temazepam (11), clonazepam (4), chlordiazepoxide (3), lorazepam (3), midazolam (2), clorazepate (1), and triazolam (1). The median BZ dose was 35 mg in diazepam equivalents, ranging from 2.5 mg to 180 mg. Slightly over half of the subjects misused BZs.

The subjects met on average 5 of the 9 DSM-III-R criteria for BZ dependence (see Table 8). The median SDS score of psychological dependence was 12, ranging from 5 to 15, suggesting that the subjects were severely dependent on BZs as defined by SDS.

Table 8. Benzodiazepine use of subjects

		Experimental group (N=39)	Control group (N=37)	*P*
Diazepam-equivalent dose, mg/d	Median (mean, range)	45.0 (51.8, 3.8-180)	30.0 (36.9, 2.5-100)	0.15[a]
BZ dose > 40mg/d (diazepam equivalences)	N (%)	20 (51)	13 (35)	0.16[b]
Duration of BZ use, months	Median (mean, range)	84 (107, 8-300)	84 (125, 24-360)	0.50[a]
Number of DSM-III-R dependence criteria met	Median (mean, range)	5 (4.7, 3-7)	5 (4.9, 3-9)	0.93[a]
Previous attempts to stop BZ use	N (%)	32 (82)	33 (89)	0.38[b]
Misuse of BZs	N (%)	25 (64)	18 (49)	0.17[b]

[a]Mann-Whitney *U*-test
[b]chi-square test

Alcohol and illicit drug use history. There were no differences between the study groups in lifetime and current alcohol use-related variables or lifetime illicit drug use-related variables (Table 9). Half of the subjects reported having problems with alcohol, 40% had been in treatment for alcohol at some time, 63% had AUDIT scores of 8 or higher indicating hazardous and harmful use of alcohol, and 26% had GGT values above the normal range. Of women, 44% had elevated AUDIT scores, while 79% of men had scores of 8 or more (*P*=0.002, chi-square test). Men also more often had a history of illicit drug use prior to the past year (*P*=0.006, chi-square test). In most cases, factors complicating benzodiazepine dependence were present (see Table 10).

Medical and psychiatric history. Subjects' self-reported medical and psychiatric histories are presented in Table 11. One-third reported having a long-lasting medical disorder. Most subjects regarded themselves as having a psychiatric disorder, 89% had at some point received psychiatric treatment, and 45% used psychiatric medications other than BZs, which were almost invariably antidepressants.

The current and lifetime psychiatric diagnoses of the subjects are presented in Table 12. Nearly all subjects had at least one additional lifetime axis I disorder diagnosed and nearly 80% had past month axis I diagnoses. Anxiety disorders, mostly social phobia and panic disorder, were the most common current diagnoses. They were diagnosed in almost half of the subjects. Mood disorders (mainly major depression and dysthymia) were nearly as prevalent, being diagnosed in 45% of subjects. The two study groups differed from each other only in the number of subjects with lifetime anxiety disorders, which were more prevalent in the control group. Past month alcohol use disorders were detected in 30% of subjects, and 64% received a lifetime alcohol use disorder diagnosis. Men had a significantly higher prevalence of current (*P*=0.031, chi-square test) and lifetime (*P*=0.018, chi-square test) alcohol use disorders than women. The SCID categorization of past month and lifetime disorders was used so that by not meeting symptomatic diagnostic criteria in the past month the subject was excluded altogether from the past month category, i.e. partial remissions were treated as remissions.

Table 9. Drinking and illicit drug use history of subjects

		Experimental group (N=39)	Control group (N=37)	*P*
Alcohol use during the last year	N (%)			0.66[a]
No use		6 (15)	5 (14)	
Sporadically		11 (28)	11 (30)	
Binges		8 (21)	8 (22)	
On 2-3 days weekly		8 (21)	11 (30)	
Daily or almost daily		6 (15)	2 (5)	
Self-reported alcohol problems	N (%)	21 (54)	16 (43)	0.36[a]
Past treatments for alcohol or illicit drug problems[b]	N (%)	15 (38)	15 (42)	0.78[a]
Ongoing treatment for alcohol problems	N (%)	8 (21)	2 (5)	0.087[c]
GGT value, males	Median (range)	56 (18-326)	41 (12-153)	0.20[d]
GGT value, females	Median (range)	26 (14-79)	25 (14-98)	0.99[d]
GGT value over the normal range	N (%)	11 (28)	9 (24)	0.70[a]
AUDIT score	Median (range)	14 (0-27)	12 (0-29)	0.84[d]
AUDIT over the normal range	N (%)	26 (67)	22 (59)	0.52[a]
Past use of illicit drugs[e]	N (%)	5 (13)	7 (19)	0.47[a]
Cigarette consumption	Median (range)	10 (0-35)	10 (0-40)	0.71[d]
Coffee consumption (cups)	Median (range)	3 (0-17)	3 (0-16)	0.98[d]

[a]chi-square test
[b]Information missing for one subject
[c]Fisher's exact test
[d]Mann-Whitney *U*-test
[e]No dependence or abuse during the past year

Table 10. Factors complicating benzodiazepine dependence in study subjects[a]

Factors complicating BZ dependence	N (%)
Current alcohol use disorder	23 (30)
Past alcohol use disorder	49 (64)
AUDIT >= 8	48 (63)
BZ dose in diazepam equivalents > 40 mg/day	33 (43)
Total	66 (87)

[a]43 subjects (57%) misused BZs

Table 11. Medical and psychiatric history of subjects

History		Experimental group (N=39)	Control group (N=37)	*P*
Medical disorder	N (%)	13 (33)	13 (35)	0.87[a]
Self-reported psychiatric disorder	N (%)	31 (79)	32 (86)	0.42[a]
Previous psychiatric treatment	N (%)	35 (90)	33 (89)	NS[b]
for suicidality		4 (10)	4 (11)	NS[b]
Use of other psychiatric medications	N (%)	19 (49)	15 (41)	0.47[a]
Use of antidepressants	N (%)	17 (44)	14 (38)	0.61[a]

[a]chi-square test
[b]Fisher's exact test

Personality disorders were detected in nearly two-thirds of the subjects. Cluster C personality disorder diagnoses were the most prevalent, followed by cluster B diagnoses. The most frequent diagnoses in cluster C were obsessive-compulsive personality disorder and avoidant personality disorder. Of cluster B diagnoses, 75% were borderline personality disorders. Many of the subjects had more than one personality disorder.

Clinical features. The clinical measures of the subjects are presented in Table 13. Subjects in the control group had higher VAS tension scores than those in the experimental group. No other differences between the groups were found. The social and occupational functioning of study subjects was only slightly impaired, yet their SCL-90 psychopathology scores were clearly higher than those for the normal Finnish population.

5.3. Implementation of treatment

Neither the average duration of treatment nor the number of treatment sessions differed between the experimental and control groups. The median duration of treatment was 32.0 (range 0-52) weeks for the experimental group and 36.6 (range 0-52) weeks for the control group (P=0.20, Mann-Whitney U-test), and the median number of sessions was 14 (range 0-42) in the experimental group and 18 (range 0-68) in the control group (P=0.49, Mann-Whitney U-test). The median frequency of sessions a week was 0.54 (range 0-1.16) in the experimental group and 0.57 (range 0-2.79) in the control group (P=0.42, Mann-Whitney U-test). In addition, an attempt was made to measure the contents of the treatment sessions in both treatment groups by questionnaire. The questionnaire was abandoned because of the ambiguousness of therapists' ratings.

Altogether 10 subjects (5 in the experimental group and 5 in the control group) received alcohol detoxification treatment during the study period. In the experimental group, 5 patients (13%) received extra medication at the time of the post-treatment interview: two received noncross-tolerant hypnotics and three received medication from a new treatment site after dropping out from the study. In the control group, 18 patients (45%) received additional psychotropic medication, some receiving more than one medication (antidepressives 12, neuroleptics 6, anxiolytics 2). The difference between the study and control groups was statistically significant (P=0.001, chi-square test).

Table 12. DSM-III-R diagnoses of subjects

	All (N=76)		Study group (N=39)		Control group (N=37)		*P*	Females (N=34)		Males (N=42)		*P*
	N	%	N	%	N	%		N	%	N	%	
Current axis I diagnoses	60	79	31	80	29	78	0.91[b]	25	74	35	83	0.30b
Substance-related disorders	23	30	15	38	8	22	0.11[b]	6	18	17	40	0.031[b]
Alcohol use disorder	23	30	15	38	8	22	0.11[b]	6	18	17	40	0.031[b]
Mood disorders	34	45	18	46	16	43	0.80[b]	19	56	15	36	0.079[b]
Major depression	21	28	12	31	9	24	0.53[b]	12	35	9	21	0.18[b]
Dysthymia	12	16	6	15	6	16	0.92[b]	6	18	6	14	0.69[b]
Bipolar type II	1	1	0	0	1	3	0.49[c]	1	3	0	0	0.45[c]
Anxiety disorders	37	49	17	44	20	54	0.36[b]	15	44	22	52	0.47[b]
Social phobia	22	29	10	26	12	32	0.51[b]	10	29	12	29	0.94[b]
Panic disorder	16	21	7	18	9	24	0.50[b]	5	15	11	26	0.22[b]
Agoraphobia	7	9	5	13	2	5	0.43[c]	1	3	6	14	0.12[c]
Simple phobia	5	7	3	8	2	5	NS[c]	4	12	1	2	0.17[c]
Obsessive-compulsive disorder	3	4	2	5	1	3	NS[c]	1	3	2	5	NS[c]
Other	3	4	3	8	0	0	0.24[c]	3	9	0	0	0.085[c]
Lifetime axis I diagnoses	72	95	36	92	36	97	0.62[c]	31	91	41	98	0.32[c]
Substance-related disorders	49	64	26	67	23	62	0.68[b]	17	50	32	76	0.018[b]
Alcohol use disorder	49	64	26	67	23	62	0.68[b]	17	50	32	76	0.018[b]
Stimulant use disorder	2	3	1	3	1	3	NS[c]	0	0	2	5	0.50[c]
Cannabis use disorder	3	4	1	3	2	5	0.61[c]	1	3	2	5	NS[c]
Poly drug use disorder	2	3	1	3	1	3	NS[c]	1	3	1	2	NS[c]
Mood disorders	47	62	23	59	24	65	0.60[b]	23	68	24	57	0.35[b]
Major depression	45	59	23	59	22	60	0.97[b]	22	65	23	55	0.38[b]
Bipolar type II	2	3	0	0	2	5	0.23[c]	1	3	1	2	NS[c]
Anxiety disorders	56	74	24	62	32	86	0.014[b]	25	74	31	74	0.98[b]
Social phobia	25	33	12	31	13	35	0.69[b]	12	35	13	31	0.69[b]
Panic disorder	34	45	14	36	20	54	0.11[b]	16	47	18	43	0.71[b]
Agoraphobia	10	13	6	15	4	11	0.74[c]	2	6	8	19	0.17[c]
Simple phobia	6	8	4	10	2	5	0.68[c]	5	15	1	2	0.084[c]
Obsessive-compulsive disorder	7	9	4	10	3	8	NS[c]	5	15	2	5	0.23[c]
Other	6	8	3	8	3	8	NS[c]	5	15	1	2	0.084[c]

Personality disorder[a]	49	64	24	62	25	68	0.58[b]	23	68	26	62	0.60[b]
Cluster A	5	7	0	0	5	14	0.024[c]	0	0	5	12	0.061[c]
Paranoid	4	5	0	0	4	11	0.051[c]	0	0	4	10	0.12[c]
Schizoid	1	1	0	0	1	3	0.49[c]	0	0	1	2	NS[c]
Cluster B	20	26	11	28	9	24	0.70[b]	12	35	8	19	0.11[b]
Borderline	15	20	7	18	8	22	0.69[b]	9	26	6	14	0.18[b]
Histrionic	6	8	3	8	3	8	NS[c]	5	15	1	2	0.084[c]
Narcissistic	3	4	3	8	0	0	0.24[c]	1	3	2	5	NS[c]
Cluster C	36	47	15	38	21	57	0.11[b]	15	44	21	50	0.61[b]
Avoidant	20	26	7	18	13	35	0.089[b]	8	24	12	29	0.62[b]
Dependent	3	4	1	3	2	5	0.61[c]	2	6	1	2	0.58[c]
Obsessive-compulsive	15	20	8	20	7	19	0.86[b]	6	18	9	21	0.68[b]
Self-defeating	6	8	2	5	4	11	0.42[c]	4	12	2	5	0.40[c]
Passive-aggressive	5	7	2	5	3	8	0.67[c]	2	6	3	7	0.83[c]
NOS	1	1	0	0	1	3	0.49[c]	0	0	1	2	0.36[c]

[a]Some of subjects diagnosed with more than one personality disorder
[b]chi-square test
[c]Fisher's exact test

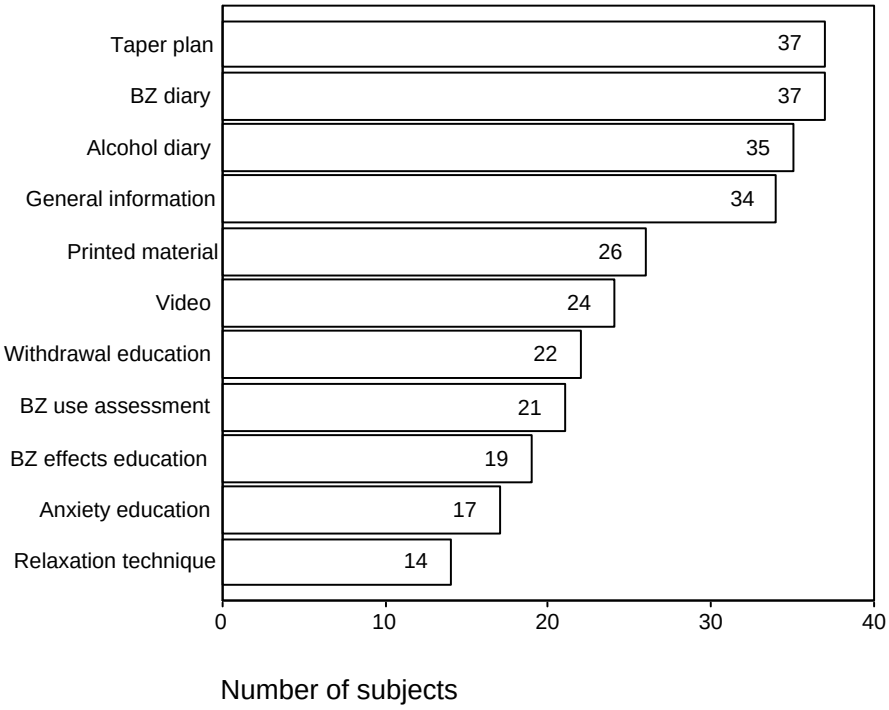
Table 13. Clinical measures of subjects

	Study group (N=39)[a]		Control group (N=37)[a]		*P*
	Mean (±SD)	Median (range)	Mean (±SD)	Median (range)	
Visual analogue scale					
Tension[c]	42.2±27.2	41.0; 0-91	56.0±27.3	57.0; 0-98	0.030[b]
Insomnia	46.3±32.4	50.0; 0-100	48.3±31.2	47.0; 0-100	0.81[c]
Inability to concentrate	54.1±29.4	52.0; 0-100	55.7±26.2	58.0; 0-100	0.80[b]
Anxiety	51.4±30.3	63.0; 0-100	53.0±32.0	58.0; 0-100	0.76[c]
VAS composite index	53.3±23.6	58.8; 2.0-94.3	48.5±20.6	49.3; 0-91.5	0.35[b]
SOFAS	73.4±5.1	74.0; 61-85	72.3±5.4	71.0; 61-85	0.39[b]
SDS	11.4±2.1	12.0; 7-15	12.1±2.6	13.0; 5-15	0.10[c]
SCL-90					
Somatization	0.97±0.60	0.83; 0.08-2.58	1.17±0.75	0.92; 0.08-2.92	0.20[b]
Obsessive-compulsive	1.37±0.73	1.40; 0.10-3.10	1.44±0.85	1.60; 0-3.00	0.69[b]
Interpersonal sensitivity	1.11±0.69	0.89; 0-2.44	1.37±0.84	1.44; 0-2.89	0.15[b]
Depression	1.64±0.74	1.62; 0.31-3.46	1.61±0.89	1.50; 0-3.46	0.86[b]
Anxiety	1.34±0.63	1.40; 0.10-2.50	1.44±0.74	1.35; 0-2.8	0.55[b]
Anger-hostility	0.78±0.82	0.50; 0-2.83	0.88±0.72	0.83; 0-2.67	0.31[c]
Phobic anxiety	1.05±0.80	1.00; 0-3.29	1.29±1.03	1.14; 0-3.29	0.43[c]
Paranoid ideation	0.88±0.83	0.67; 0-3.67	0.99±0.61	1.08; 0-2.17	0.20[c]
Psychotism	0.54±0.51	0.40; 0-2.00	0.68±0.47	0.68; 0-1,40	0.16[c]
General symptomatic index	1.14±0.51	1.13; 0.28-2.23	1.27±0.62	1.29; 0.11-2.43	0.34[b]
Health-related quality of life					
Health perceptions	54.52±20.61	55.00; 20-100	52.97±18.87	50.00; 20-85	0.73[b]
Energy/vitality	39.38±20.73	40.0; 4-80	37.19±20.70	36.0; 0-84	0.65[b]
Cognitive function	58.82±19.36	60.0; 25-100	55.41±21.90	55.0; 15-100	0.48[b]
Alertness behavior	70.33±17.60	70.40; 40.0-100.0	63.82±27.47	69.76; 14.5-100.0	0.23[b]
Home management	57.09±28.02	56.67; 10.0-100.0	55.09±25.57	53.33; 3.3-100.0	0.75[b]
Social interaction	62.81±25.85	67.5; 7.5-100.0	57.34±22.28	57.5; 10.0-100.0	0.33[b]
Life satisfaction	3.28±1.30	3.00; 1-7	3.43±1.38	3.00; 1-7	0.56[c]

[a]Total number on which percentages are based varies because of missing data for some subjects
[b]t-test
[c]Mann-Whitney *U*-test

Figure 3 displays the 11 measured components of the experimental treatment. On average, the subjects received 70% of the defined treatment components. This rate remained consistent during the study period. Exclusion of early dropouts from the analysis did not change the rate.

Figure 3. Implementation of experimental treatment[a] *(N=39)*



[a]Two subjects dropped out before entering treatment

5.4. Reasons for dropping out

Twenty-one subjects (54%) in the experimental group and 11 (30%) in the control group dropped out from treatment. The difference was significant (*P*=0.033, chi-square test). When reanalyzed after excluding subjects who did not participate in the treatment or dropped out for reasons unrelated to the treatment (e.g. leaving the geographic area, medical problems, work, studies), the difference in treatment completion was no longer significant (*P*=0.105, chi-square test). The reasons for dropping out are listed in Figure 1. In both groups, the dropouts were equally distributed throughout the treatments. One subject who had been randomized to the control group but had not participated in the treatment committed suicide a few months later.

Dropping out of treatment was significantly associated with personality disorder cluster B (*P*=0.003, chi-square test), with borderline personality disorder, which was the most prevalent cluster B disorder (*P*=0.032, chi-square test), with low HRQOL life satisfaction scores (*P*=0.010, trend test), and with misuse of BZs *(P*=0.022, chi-square test). Of subjects with

cluster B personality disorder, 70% dropped out of treatment, while only 30% of other subjects did so.

5.5. Alcohol use

No baseline imbalance in reported alcohol use, GGT values, or AUDIT scores was observed between the experimental and control groups. Therefore, changes in these measurements were analyzed without controlling for baseline values.

At the end of the follow-up phase, 30% of experimental group subjects and 32% of controls reported a decrease in alcohol consumption, and 18% and 25%, respectively, reported an escalation (*P*=0.75, chi-square test). There was no median change in the AUDIT of the experimental group (range -14 to +14) or the control group (range -23 to +23) (*P*=0.96, Mann-Whitney *U*-test). The median change of GGT values in the experimental group was 1 (range -988 to +45) and in the control group -1 (range -89 to +87) (*P*=0.66, Mann-Whitney *U*-test).

At the end of the follow-up, alcohol use-related data were obtained, depending on the variable, for 70-80% of BZ-free subjects, 66-86% of subjects with significant dose decreases, and 61-74% of subjects with smaller decreases. The median GGT decrease was 0 (range -988 to +69) U/l in the group with no more than a 50% BZ dose decrease, 2.5 (range -150 to +69) U/l in the group with over a 50% dose decrease, and 3.0 (range -21 to +87) U/l in the BZ-free group (*P*=0.30, Kruskall-Wallis test). The median decreases in the AUDIT scores were -3 (range -23 to +14), 0 (range -8 to +12), and 1.5 (range -4 to +23), respectively (*P*=0.21, Kruskall-Wallis test). Forty-eight percent, 50%, and 38%, respectively, reported no changes in alcohol use frequency during the study (*P*=0.78, chi-square test). No alcohol-related baseline differences were present between these three groups.

The highest alcohol consumption at the end of the follow-up was found in the group that was least successful with BZ withdrawal, i.e. did not decrease their BZ doses or decreased by no more than 50%. They most often drank nearly daily (22% compared with 3% in the group with more than a 50% decrease and 0% in the BZ-free group; *P*=0.03, chi-square test), most often had GGT values over the normal range (48%, 22%, and 0%, respectively; *P*=0.04, chi-square test) or AUDIT scores over 8, indicating harmful and hazardous use of alcohol (79%, 56%, and 25%, respectively; *P*=0.03, chi-square test).

5.6. Other medications at follow-up

At the end of the follow-up, no differences between the two study groups were found in use of any psychiatric medications other than BZs (*P*=0.36, chi-square test). While 45% of the subjects had used other medications before the beginning of the study, 43% used them at the end of the follow-up. Furthermore, at the follow-up, 46% of subjects with BZ use and 35% of BZ-free subjects had other psychiatric medications, and 42% of subjects with BZ use and 35% of BZ-free patients were taking antidepressants.

5.7. Validating information

At the end of the treatment phase, urine samples were obtained from 64 subjects (84%) and serum samples from 59 subjects (78%). For one individual, the samplings were performed late and were therefore omitted from the analyses. All who reported not using BZs were negative in both urine and serum tests (Table 14).

Table 14. Concordance between reports of BZ use and urine (N=63) and serum (N=58) analyses

	Interview: use	Interview: no use	% agreement[a]	Kappa
Urine positive	38	0		
Urine negative	12	13	81	0.44
Serum positive	38	0		
Serum negative	7	13	89	0.50

[a]Proportion of agreement between self-reports and analyses

Fifty-eight subjects (76%) provided both a serum sample and reported their BZ preparations and dosages. Of these, 17 (29%) had discrepant results between reported BZ use and BZ detected in serum. Additional BZ compounds to those reported were found in 7 (12%) of the serum samples. In the other cases, reported BZ use was not confirmed by analyses.

Both an interview and patient records were obtained from 49 subjects. Agreement between the documents from treatment settings and the subject reports of BZ doses was good (intraclass correlation coefficient 0.98, 95% Cl 0.968-0.990). The mean difference ± 2 SD (i.e. 95% agreement limit) was 2.0 mg ± 19.8 mg in diazepam-equivalent doses. There were only six cases in which the difference was over 5 mg/day.

At the six-month follow-up assessment, urine and serum samples were obtained from 54 (71%) subjects (see Table 15). Four subjects who reported not using BZs were positive in the urine screen. As assessed by the kappa statistic, the agreement was moderate (kappa 0.47). In the serum tests, three subjects were positive, although they had reported not using BZs (kappa 0.64). Additional BZ compounds to those reported were found in 9 (17%) of the serum samples. Both an interview and patient records were obtained from 38 subjects. Agreement between the documents from treatment settings and the subject reports of BZ doses was good (intraclass correlation coefficient 0.96, 95% Cl 0.93-0.98. The mean difference ± 2 SD (i.e. 95% agreement limit) was -1.8 mg ± 23.3 mg in diazepam-equivalent doses. In nine cases, the difference was over 5 mg/day.

At the 12-month follow-up assessment, urine samples were obtained from 50 subjects (66%) and serum samples from 51 subjects (67%) (Table 16). One subject was found to be urine- and serum-positive, despite reporting not using BZs, and was therefore regarded in the outcome analyses as a BZ user. For the urine screens, kappa was 0.58, and for the serum tests 0.81. No differences in the demographic data, diagnoses, or BZ- and alcohol-related variables were found between the subjects who could be tested for BZs and those who could not. Additional BZ compounds to those reported were found in 5 (10%) of the serum samples. Both an interview and patient records were obtained from 32 subjects. Agreement between the documents from treatment settings and the subject reports of BZ doses was good (intraclass correlation coefficient 0.99, 95% Cl 0.97-0.99). The mean difference ± 2 SD (i.e.

95% agreement limit) was 2.1 mg ± 12.3 mg in diazepam-equivalent doses. In six cases, the difference was over 5 mg/day.

Table 15. Concordance between reports of BZ use and urine (N=54) and serum (N=54) analyses at the six-month follow-up

	Interview: use	Interview: no use	% agreement[a]	Kappa
Urine positive	25	4		
Urine negative	10	15	74	0.47
Serum positive	30	3		
Serum negative	6	15	83	0.64

[a]Proportion of agreement between self-reports and analyses

Table 16. Concordance between reports of BZ use and urine (N=50) and serum (N=51) analyses at the 12-month follow-up

	Interview: use	Interview: no use	% agreement[a]	Kappa
Urine posit.	27	1		
Urine negat.	9	13	80	0.58
Serum posit.	34	1		
Serum negat.	3	13	92	0.81

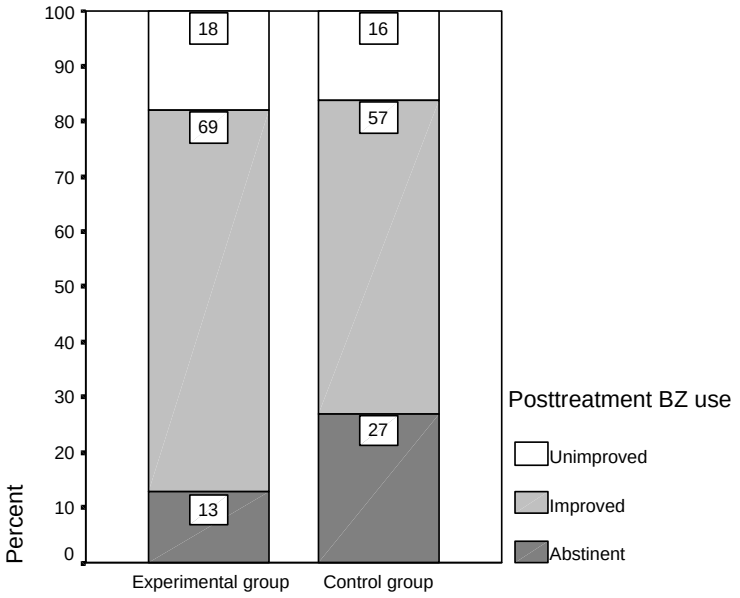
[a]Proportion of agreement between self-reports and analyses

5.8. Short-term outcome

Figure 4 displays the post-treatment results. Data on whether the subjects continued to use BZs were obtained from all 76 subjects, either by interviews (N=61; 80%) or by treatment documents (N=64; 84%). The number of subjects who successfully discontinued their BZ medication was 5 in the experimental group and 10 in the control group (*P*=0.12, chi-square test). A total of 32 subjects (82%) in the experimental group and 31 subjects (84%) in the control group either decreased their dosage or discontinued their BZ medication. No significant differences were found between the treatment groups in rates of subjects who were BZ-free, had decreased their BZ doses, or had not decreased their doses (*P*=0.30, chi-square test).

The median changes in dosages from the baseline did not differ significantly between the two groups (*P*=0.12, Mann-Whitney *U*-test). In the experimental group, the median dose reduction was 60%, ranging from -62.5% to +100.0%. In the control group, the median reduction was 81.2%, ranging from -150.0% to +100.0%. Because there was an imbalance, albeit not significant, between the initial BZ doses in the two study groups, an ANCOVA using logarithms of the baseline and post-treatment doses was also performed, with similar results (F=2.87, df=1, *P*=0.094). Therefore, to enable a more straightforward analysis, the unadjusted Mann-Whitney *U*-test with the simpler interpretation was chosen.

Figure 4. Proportions of abstinent, improved, and unimproved patients at the post-treatment evaluation



In the three control treatment settings, the proportions of BZ-free subjects after treatment were 6/20 (30%), 1/6 (17%), and 3/11 (27%) (*P*=0.89, chi-square test). The corresponding median decreases of the doses were 69.6% (-150% to +100%), 86.6% (+33% to +100%), and 81.3% (0% to +100%) (*P*=0.86, Kruskall-Wallis test).

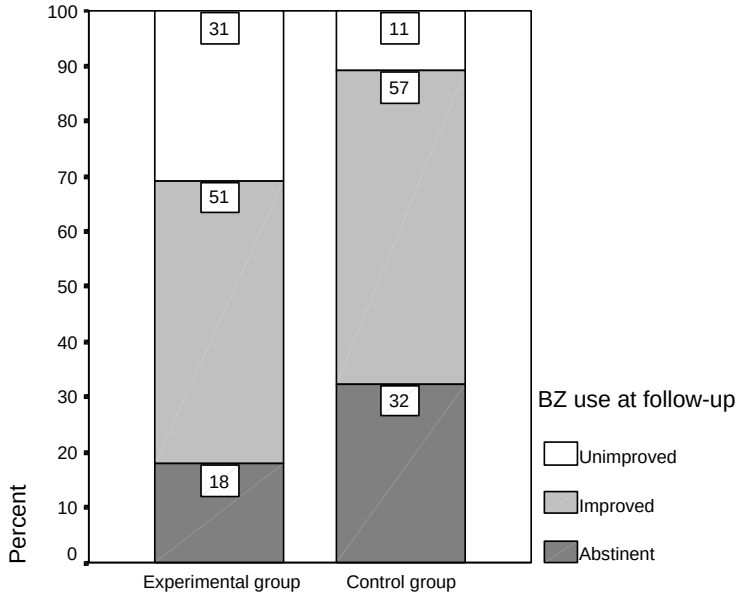
5.9. Long-term outcome

At the six-month follow-up assessment, interview data or treatment documents for BZ use were obtained for 68 subjects (89%) and at the 12-month follow-up for 73 subjects (96%). Two subjects were dead. One did not attend any treatment sessions and committed suicide a few months after randomization to the study. The other subject discontinued BZ use but died for an unrelated reason before the 12-month follow-up assessment. The data for these subjects was carried forward in the analyses. The end-point status of one subject could not be assessed by interview or by treatment documents; this subject did not attend any treatment and was regarded as using BZs at the follow-up points. The subjects who could be interviewed (N=61; 80%) and those who could not be interviewed at the end of the follow-up were similar with respect to the baseline variables.

No differences were found in outcome measures between the experimental and control groups. Fifteen subjects (20%) were BZ-free after the treatment phase, but 19 (25%) were BZ-free at the 12-month follow-up, 7 in the experimental group and 12 in the control group (*P*=0.61, Likelihood ratio test). The proportions of abstinent, improved (decreased dose), and unimproved cases (no dose decrease) at the 12-month follow-up are presented in Figure 5

(*P*=0.071, chi-square test). Of the 57 subjects who were still using BZs at the 12-month assessment, 72% used doses lower than those at pre-treatment, with 46% using doses more than 50% lower than pre-treatment doses. Five of the 15 individuals who were abstinent at the post-treatment evaluation had resumed BZ use at the 12-month assessment, but nine other subjects had stopped using BZs during the follow-up period. In addition, 11 subjects had after the post-treatment assessment discontinued BZ use but resumed use before the last follow-up assessment.

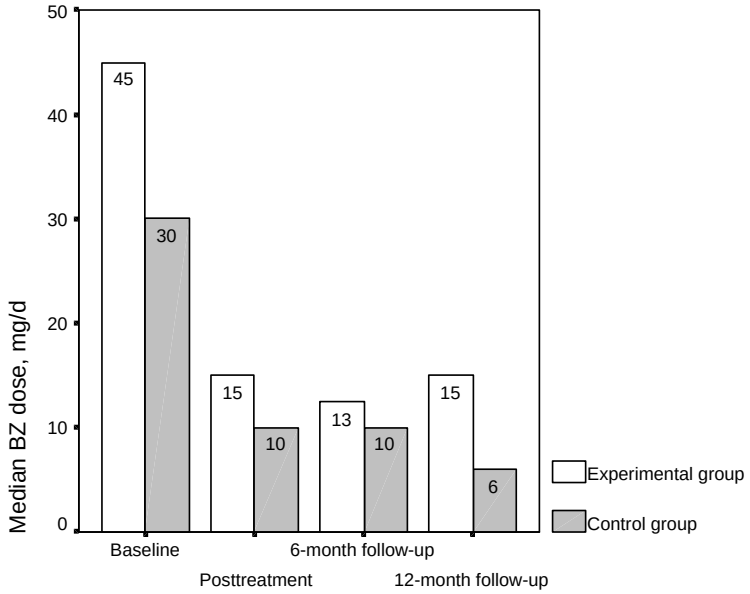
Figure 5. Proportions of abstinent, improved, and unimproved patients at the follow-up evaluation as compared with baseline



The doses in the two treatment groups at the various assessment times are presented in Figure 6. No differences were found in the dose changes between the groups during the follow-up period (Repeated measures ANCOVA of log data, logarithm of baseline BZ dose as a covariate; F=1.31, df=1,73 with Huynh-Feldt correction, *P*=0.27). For the entire study group, the median decrease of daily BZ dose from post-treatment dose was 0 (range -60 to +116.7) mg in diazepam equivalents, while the median decrease from the pre-treatment dose was 16.1 (range -60 to +160) mg.

The BZ dose changes in subjects with initially high doses (doses over 40 mg in diazepam equivalents) and in those with initially low doses were examined separately. For subjects with high pre-treatment doses, the median decrease from the pre-treatment dose was 31.25 (range -60 to +160) mg, and for subjects with low pre-treatment doses, it was 10 (range -25 to +40) mg. At the end of the study, the median dose of subjects with initially high doses was 30 (range 0 to +140) mg.

Figure 6. Median BZ doses in the study groups



5.10. Predictors of successful benzodiazepine discontinuation

Several baseline variables in univariate analyses were associated with successful discontinuation of BZs: a higher HRQOL life satisfaction score (P=0.001, trend test), a lower BZ dose (P=0.003, trend test), no BZ misuse (P=0.009, chi-square test), no previous withdrawal attempts (P=0.010, Fisher's exact test), schooling of 9 years or less (P=0.010, Fisher's exact test), lower anxiety self-rated by VAS (P=0.019, trend test), higher HRQOL energy/vitality score (P=0.023, trend test), lower number of BZ dependence diagnostic criteria (P=0.036, trend test), and lower SDS score (P=0.048, trend test). Of these, education was discarded from the logistic regression analysis because no theoretical relationship existed between low level of education and successful BZ discontinuation. All patients with cluster B personality disorder failed to discontinue BZ use (P=0.008, Fisher's exact test). This resulted in an excessively large estimated odds ratio in the logistic regression analysis, thus the personality variable was also omitted from the analyses.

The best logistic regression model of BZ discontinuation (model chi-square=15.48, df=3, P=0.0014, correct predictions 85.5%) included no previous withdrawal attempts (P=0.012, OR=7.01, 95% CI for OR=1.55 to 31.72), low BZ dose (P=0.024, OR=4.50, 95% CI for OR=1.21 to 16.64), and being a member of the control group. The contribution of control group membership was not significant (P=0.071, OR=3.58, 95% CI for OR=0.89 to 14.33).

Several of the potential predictor variables covaried. A higher dose of BZs was associated with misuse of BZs (P<0.0005, trend test), a higher SDS score (P=0.003, trend test), and a higher number of DSM-III-R BZ dependence criteria met (P=0.002, trend test). Subjects with previous attempts to stop using BZs had higher SDS scores (P=0.002, trend test) and met a

greater number of BZ dependence criteria (P=0.01, trend test). Misuse of BZs was associated with a higher number of DSM-III-R BZ dependence criteria met (P<0.0005, trend test). In addition, lower levels of education were associated with higher scores of HRQOL life satisfaction (P=0.001, trend test).

5.11. Predictors of staying benzodiazepine-free

The following seven variables were associated with maintenance of BZ-free status during the follow-up period: a lower initial BZ dose (P<0.0005, trend test), higher life satisfaction at baseline (P=0.001, trend test), a lower number of DSM-III-R BZ dependence criteria met (P=0.002, trend test), completion of the treatment phase (P=0.004, Fisher's exact test), lack of previous withdrawal attempts (P=0.007, Fisher's exact test), no BZ misuse (P=0.017, Fisher's exact test), and lower baseline self-rated anxiety (P=0.020, trend test). Of these, the six baseline variables had already been found to be associated with treatment outcome.

The best logistic regression model (model chi-square=28.06, df=4, P<0.0005, correct predictions 93.0%) included higher life satisfaction (P=0.012, OR=26.14, 95% CI for OR=2.03 to 337.50), no previous withdrawal attempts (P=0.010, OR=17.48, 95% CI for OR=1.97 to 155.33), a lower BZ dose (P=0.0045, OR=24.14, 95% CI for OR=2.69 to 217.01), and membership in the control group. The contribution of control group membership was not significant (P=0.50, OR=2.06, 95% CI for OR=0.26 to 16.49).

Of the potential predictors, lower life satisfaction was associated with dropping out from treatment (P=0.010, trend test) and with a higher anxiety score (P<0.0005, trend test). In addition, lower life satisfaction was found to be associated with several measures of a psychopathologic condition: current depressive disorder (P<0.0005, trend test), higher SCL-90 scores (P=0.002, trend test), lower self-rated functioning and inability to concentrate (P<0.0005, trend test, and P=0.004, trend test, respectively), a higher number of axis I diagnoses (P=0.005, trend test), personality disorder cluster B (P=0.017, trend test), and higher AUDIT scores (P=0.027, trend test).

5.12. Psychiatric symptoms, social and occupational functioning, and quality of life

Changes in the SOFAS scores were not analyzed because the average scores were maintained throughout the study. At baseline, subjects had only a slight impairment in functioning as assessed by the SOFAS.

Changes in SCL-90, VAS, and HRQOL scores were analyzed by ANCOVA. No significant differences were found in any of the measurements between the two study groups either after the treatment or after the follow-up (Table 17). The results were similar in additional analyses without replaced values or by MANCOVA.

For the entire study sample, significant improvements were found in symptom levels and in many of the quality of life measures for the treatment phase. For the follow-up phase, changes were smaller, and only the SCL-90 score decreased significantly (Table 18). Additional analyses by using Wilcoxon's paired tests confirmed the results.

For the three groups based on BZ use during follow-up (no use during follow-up, decrease of dose over 50% at the end of follow-up, and decrease of 50% or less at the end of follow-up), some significant differences were found between the subjects who decreased their BZ

doses more than 50% and those who decreased them less (Figure 7). The analyses were performed by ANCOVA. Differences were found in the adjusted follow-up HRQOL energy/vitality (mean difference 12.8, 95% CI 1.5 to 24.0, *P*=0.02 in a pairwise comparison between decrease > 50% and decrease =< 50% at follow-up), home management (mean difference 20.4, 95% CI 5.7 to 35.0, P=0.003 in a pairwise comparison between decrease > 50% and decrease =< 50% at follow-up), and life satisfaction scores (mean difference 1.0, 95% CI 0.2 to 1.9, P=0.01 in a pairwise comparison between decrease > 50% and decrease =< 50% at follow-up). In an additional multivariate analysis, the *P* values for the mean differences in the pairwise comparisons (Bonferroni adjustment) were P=0.049, P=0.045, and P=0.05, respectively. The multivariate F was nonsignificant.

Table 17. Differences between change scores in the two study groups (SCL-90 = Symptom Checklist-90 total score; VAS = visual analogue scale, composite score for tension, sleep, concentration, and anxiety; HRQOL = health-related quality of life)[a]

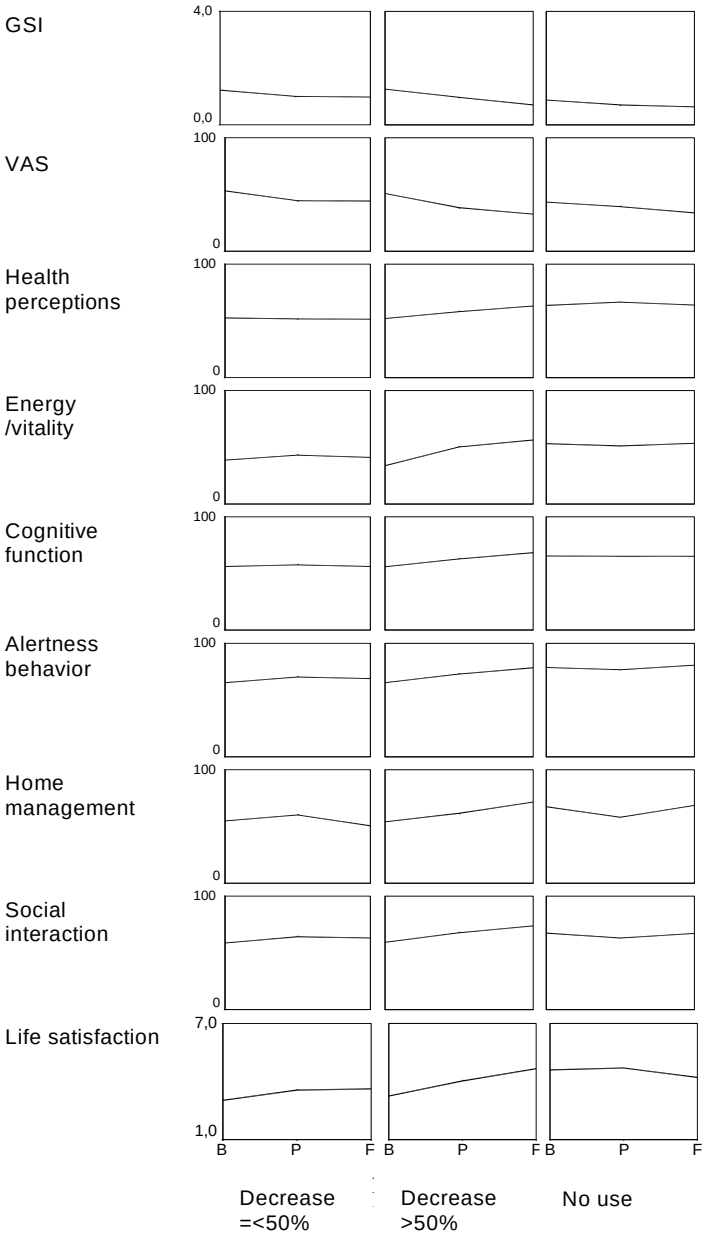
	Treatment phase				Follow-up phase			
	N	Difference	95% CI	*P*	N	Difference	95% CI	*P*
SCL-90	76	-0.06	-0.32 to 0.20	0.64	69	-0.10	-0.35 to 0.14	0.40
VAS	76	-0.38	-10.55 to 9.79	0.94	69	-2.99	-13.58 to 7.60	0.57
HRQOL health perceptions	72	-1.75	-10.19 to 6.68	0.68	66	-2.61	-11.23 to 6.01	0.55
HRQOL energy/vitality	72	3.60	-5.20 to 12.41	0.42	66	-1.42	-10.61 to 7.77	0.76
HRQOL cognitive function	72	3.69	-2.32 to 9.71	0.22	66	-0.17	-9.31 to 8.96	0.97
HRQOL alertness behavior	72	2.50	-6.01 to 11.01	0.56	66	2.21	-7.07 to 11.48	0.64
HRQOL home management	71	7.23	-2.41 to 16.86	0.14	65	-3.15	-15.04 to 8.74	0.60
HRQOL social interaction	72	8.58	-0.60 to 17.76	0.07	66	-1.49	-11.66 to 8.68	0.77
HRQOL life satisfaction	71	0.06	-0.47 to 0.58	0.83	63	0.06	-0.60 to 0.72	0.85

[a]ANCOVA, baseline measurements as covariates in the analyses of the treatment phase; post-treatment measurements as covariates in the analyses of the follow-up phase

Table 18. Paired t-tests on measures of the subjects (SCL-90 = Symptom Checklist-90 total score; VAS = visual analogue scale, composite score for tension, sleep, concentration, and anxiety; HRQOL = health-related quality of life; for SCL-90 and VAS, high scores indicate higher levels of symptoms; for HRQOL, high scores indicate higher functioning and well-being)

Measure	Treatment phase					Follow-up phase				
	N	Change score	SD	95% CI	*P*	N	Change score	SD	95% CI	*P*
SCL-90	76	0.25	0.58	0.12 to 0.38	< 0.0005	69	0.16	0.61	0.01 to 0.31	0.03
VAS	76	9.83	25.11	4.09 to 15.57	0.001	69	3.83	25.42	-2.28 to 9.94	0.22
HRQOL health perceptions	72	-2.55	19.10	-7.04 to 1.94	0.26	66	-2.48	18.32	-6.99 to 2.02	0.28
HRQOL energy/vitality	72	-9.22	21.56	-14.29 to -4.16	0.001	66	-4.55	20.94	-9.69 to 0.60	0.08
HRQOL cognitive function	72	-3.26	14.15	-6.59 to 0.06	0.05	66	-3.86	19.78	-8.73 to 1.00	0.12
HRQOL alertness behavior	72	-4.97	20.04	-9.68 to -0.26	0.04	66	-5.19	20.89	-10.32 to -0.05	0.05
HRQOL home management	71	-3.77	23.19	-9.26 to 1.71	0.17	65	-4.19	25.21	-10.44 to 2.05	0.18
HRQOL social interaction	72	-4.98	22.35	-10.23 to 0.28	0.06	66	-4.69	24.13	-10.62 to 1.24	0.12
HRQOL life satisfaction	71	-0.54	1.22	-0.82 to -0.25	< 0.0005	63	-0.32	1.55	-0.71 to 0.07.	0.11

Figure 7. Changes in the scores for groups based on benzodiazepine use during the follow-up period (B = pre-treatment, P = post-treatment, F = follow-up, GSI = Symptom Checklist-90 general symptomatic index, VAS = visual analogue scale; for GSI and VAS, high scores indicate higher levels of symptoms; for the remainder, high scores indicate higher functioning and well-being)



6. DISCUSSION

This study focused on an area that has thus far not been examined thoroughly; it highlighted the difficulties of BZ withdrawal in subjects with high dose dependence and concurrent alcohol problems. The subjects did not fare better after gradual tapering with cognitive-behavioral treatment when compared with conventional treatment. Of the entire sample, 20% completely discontinued BZ use, and an additional 63% were able to reduce their use. The treatment results were maintained in both treatment groups. Those with high pre-treatment BZ doses also generally lowered their usage to a clinically relevant level, i.e. to therapeutic levels. Pre-treatment low BZ dose and lack of previous withdrawal attempts predicted successful treatment outcome, and low BZ dose, no previous withdrawal attempts, and high life satisfaction at baseline predicted long-term success. No patients with cluster B personality disorder managed to discontinue BZ use during the withdrawal treatment. Concurrently with BZ dose decreases, improvements in subjects' symptom severity and quality of life occurred.

6.1. Methodological considerations

The study was conducted as a randomized clinical trial. A clinical trial is a planned experiment in human beings that is designed to evaluate the effects of one or more forms of treatment (Altman, 1991). Among the various types of studies, clinical trials generally provide the best evidence of possible treatment effects. The main characteristic of a clinical trial is the comparison of groups of subjects who differ only with respect to treatment. The study's design and analysis therefore aim to eliminate any factors that distort events or observations during the trial. Central features in designing a clinical trial are ensuring adequate sample size, random allocation, the maximum degree of blindness possible under the treatment conditions, thorough follow-up, and appropriate analysis focused on differences between groups.

Internal validity of the study. The term internal validity refers to the ability of the study findings to represent the true causal relationship between the intervention and the outcome of the study. Besides the intervention itself, other treatment and patient factors also contribute to treatment outcome. Moreover, other kinds of factors can affect the internal validity of a study, including the therapeutic effects of measuring and interviewing, and regression to the mean (e.g. those using BZs the most are prone to decrease use the most), but these act similarly on all treatments (Koski-Jännes, 1991).

The power of the study to detect a 33% difference in taper outcome between the two treatment groups in a two-tailed test at the 5% level was 80%. In addition to the power calculations, other considerations in deciding the size of the study exist. The capacity of the A-clinics at Helsinki to respond to new patients was a main constraint. The staff of four regional A-clinics was calculated to be required to treat the planned number of subjects. As a consequence, the subjects in the experimental group received uniform treatment at one of the clinics, whereas the three control groups received three different programs. These were mainly supportive treatments; in some cases, brief psychotherapy with strength perspective, and in other cases, cognitive approaches, together representing the spectrum of routine treatment available at A-clinics in Helsinki. Treatment of the experimental and control groups in different settings probably served to diminish contamination of the treatments or compensatory rivalry between treatments. However, using three control group clinics made

the control treatment more heterogeneous, which was not ideal for revealing treatment-related differences.

After randomization, the two treatment groups were comparable with each other in all essential variables, so there was no patient selection bias. Further, randomization served to lessen the probability of selective differences in maturation processes (e.g. natural recovery), in changes in life circumstances during the study period, or in interactions of these between the groups.

A standardized treatment protocol for the experimental treatment was not used, but a manual was provided that the therapists were instructed to utilize in tailoring the techniques to meet the needs of individual subjects. A uniform manualized treatment would have been the strictest way of controlling the experimental treatment (Dobson and Shaw, 1988). However, rigid approaches that prescribe session-by-session interventions have been criticized as being incompatible with the cognitive-behavioral therapy emphasis on identifying the specific factors that maintain the problems in individual patients and tailoring interventions to those needs (Wilson, 1996).

Generally, the experimental group subjects received 70% of the treatment components to be measured. In studies of cognitive-behavioral treatment, those receiving a minimum of 70% to 85% of the planned therapy sessions have usually been considered completers (Tang and DeRubeis, 1999). Our rate of treatment completion was consistent with these studies and also comparable with figures in previous research in psychotherapy and in BZ-dependent and alcohol-dependent subjects (Luborsky et al., 1985; Sanchez-Craig et al., 1987; Carroll et al., 1998). However, some of the treatment components were carried out less often than others. Assessment of BZ functions, for instance, was implemented in only 54% of cases. This raises the question of whether the therapists conformed better to some intervention strategies than to others. Thus, although the implementation of the treatment was generally satisfactory, some bias may be present in the content of the experimental treatment.

There were also some factors concerning the practices of the control clinics that could affect the discriminability of the control treatment from the experimental treatment. During the study period one of the control clinics altered its treatment practices. Some cognitive approaches were adopted, and supportive group treatment was offered to 5 of the 20 subjects treated there. Therefore, the treatment at this clinic involved components similar to the experimental treatment, possibly diminishing the chances of finding treatment effects. In addition, the use of diary keeping for monitoring BZ dosages in both experimental and control conditions may have brought the two study conditions closer to each other. Diary keeping is a cognitive approach of self-monitoring that is assumed to alleviate symptomatology (Golombok and Higgitt, 1993).

The effects of therapist heterogeneity were controlled for by using several therapists at each clinic (Luborsky et al., 1985; Carroll et al., 1994). While differences in treatment results between individual therapists were not measured, no differences were found between the three control clinics. Between the experimental and control treatments, no difference in treatment dropout due to dissatisfaction or unknown reasons was present.

Altogether 21 subjects (54%) in the experimental group and 11 subjects (30%) in the control group dropped out from treatment after the randomization. The dropouts were equally distributed throughout the treatments, and there was no selective loss in relation to the clinics involved or the baseline characteristics of subjects. Reasons unrelated to the treatment, i.e. changes in subjects' life circumstances, accounted for the significantly greater dropout rate in

the experimental group. Moreover, excluding these unrelated dropouts from the analyses did not change outcome results.

Towards the end of treatment, about half of the control subjects received additional medications for psychiatric symptoms, but this use was not related to outcome. During the follow-up period some of the subjects continued to receive treatment at the study clinics, and among them, the subjects at the control treatment clinics received more intensive treatment. When the subjects who continued to attend treatment during the follow-up were omitted from outcome analyses, the results were similar to those obtained for the entire subject group. Hence, crossover bias is unlikely.

Follow-up of the study groups was successful. Immediate treatment outcome could be assessed for all study subjects. After the follow-ups, outcome data for most of the subjects was gathered, either via interviewing the subjects or acquiring their treatment documents, and an adequate amount of the data could be validated by serum tests. Unfortunately, alcohol-related variables were obtained less frequently, partly because of problems with the AUDIT questionnaire (some of the subjects failed to notice that the form was two-sided) and partly because of incompletely obtained serum samples.

External validity of the study. The term external validity refers to the extent to which the findings from a particular study can be generalized to other circumstances. Most clinical trials are designed to investigate narrowly defined patient groups in order to diminish the effects of patient variation on outcome, thereby strengthening the possibility of finding difference between groups (Goodman, 1993). The findings may thus not be applicable to other types of patients. Frequently used exclusion criteria, such as psychiatric or emotional problems, noncompliance or lack of motivation, serious medical problems, social instability, or residential instability, render large proportions of patients ineligible to participate (Humphreys and Weisner, 2000*)*. Further, findings of studies conducted in special settings may not be transferable to general or routine settings. Increasing internal validity often impairs external validity and vice versa. In other words, when designing clinical studies, the precision of methods must be balanced against the representativeness of treatments and the generalizability of results.

This study was designed to examine the clinical utility of a BZ withdrawal treatment program in routine clinical settings. It was conducted at public sector outpatient clinics for alcohol- and drug-dependent subjects (A-clinics) without providing any additional resources or any specially trained staff. It involved subjects frequently seen in clinical practice, i.e. subjects with BZ dependence and concomitant alcohol use disorders and other psychiatric disorders. Because alcohol use disorders are among the most common comorbid diagnoses for BZ dependence (Regier et al., 1990), widening the study to this combination was deemed reasonable. The exclusion criteria were not extensive, excluding only those who could not attend outpatient treatment or would attend other kinds of treatment during the study. The results are therefore expected to be generalizable to clinical practice throughout Finland.

Most of the subjects screened for the study (100/120) subsequently enrolled. No selective loss of subjects was observed during the screening procedure before the baseline assessment (Figure 2), indicating that the sampling was representative and further supporting the generalizability of the study.

Limitations of the study. The main limitations of the study were the small sample size, which did not enable revealing smaller differences between the study groups or possible subgroup differences (see page 73); constraints on the implementation of the experimental treatment (see page 74); possible overlap in study treatments (see page 74); and subject heterogeneity, which while enhancing the external validity of the study, probably diminished the chances of getting positive results.

6.2. Treatment attrition

Fifty-four percent of the experimental group and 30% of the control group did not complete the treatment. High dropout rates have also been common in earlier BZ discontinuation studies (Higgitt et al., 1987; Sanchez-Craig et al., 1987; Murphy and Tyrer, 1991; Tyrer et al., 1996). Dropping out of treatment was associated with personality disorder cluster B, low life satisfaction scores, and BZ misuse. Of subjects with a cluster B personality disorder, 70% dropped out of treatment compared with 30% of other subjects. For chronic BZ users, previous evidence indicates that patients with dependent personality characteristics are prone to drop out from treatment early before experiencing any withdrawal difficulties (Schweizer et al., 1998). The present study suggests that subjects who have cluster B personality disorders need to have extra attention focused on their personality disorder to improve their withdrawal treatment outcomes.

Four subjects subsequently chose not to enroll in the treatment (two in the experimental group and two in the control group). Of the experimental group subjects, one was diagnosed with social phobia and borderline personality disorder and the other with dysthymia, alcohol dependence, and avoidant personality disorder. They both rescinded their decision to participate in the study, choosing to continue with their former psychiatric outpatient treatments. Their decisions were unrelated to the results of randomization. In the control group, one subject diagnosed with social phobia was lost in the follow-up. The other subject sought withdrawal treatment for alcohol dependence and committed suicide shortly thereafter.

Significantly more subjects dropped out from treatment in the experimental group than in the control group. However, when analyzed after excluding subjects who did not participate in the treatment or dropped out for reasons unrelated to treatment, the difference in treatment completion was no longer significant.

6.3. Treatment outcomes

Twenty percent (13% in the experimental group and 27% in the control group) of the subjects completely discontinued their BZ use, and 25% (18% in the experimental group and 32% in the control group) were BZ-free at the 12-month follow-up. Our results approach those of earlier studies in chronic users who had experienced difficulty in previous attempts to reduce their medication (Higgitt et al., 1987; Sanchez-Craig et al., 1987). However, the present study included subjects who drank alcohol more heavily and generally used higher doses of BZs than the subjects in previous research, so the studies are not fully comparable. To improve treatment outcomes, our study patients could have gained from additional services provided to deal with such factors as medical, financial, psychiatric, family, or legal problems (McLellan et al., 1997).

Eighty percent of the experimental group subjects and 84% of the controls either discontinued or reduced their BZ use during the study period. The median reduction from the pre-taper dosage was 60% in the experimental group and 81% in the control group. Sanchez-Craig et al. (1987) found that 62% of their subjects either discontinued completely or had BZ plasma level reduction of at least 50%. In Higgitt et al. (1987), 86% of subjects discontinued or reduced their medication by over 50%, whereas the corresponding figures in our study were 54% of the experimental group and 59% of controls. In a nonselected general practice long-term user population, Onyett and Turpin (1988) found a 59% reduction in dosage with cognitive-behavioral group treatment. Thus, the overall reductions in BZ doses in our study were similar to those in previous research.

Subjects with high pre-treatment BZ doses lowered their usage to a clinically significant level. While regression to the mean may explain the greater dose decrease for this group than for subjects with initially lower doses, it is noteworthy that at the end of follow-up the median BZ use in the former group was at a therapeutic level. Achieving therapeutic dosages may imply a better control over BZ use or a reduced tolerance to BZs after treatment. These results raise the question of whether dose decrease is an adequate goal in BZ dependence. Previous research in this area is scant. Long-term therapeutic-dose BZ users tend not to increase their dosages within a 3- to 5-year period after screening for or participation in a BZ discontinuation treatment (Holton et al., 1990, Rickels et al., 1991), but certainly some subpopulations do develop uncontrolled use over a longer period (Allgulander et al., 1984; Woods et al., 1992; Griffiths and Weerts, 1997). Subjects with current drug problems belong to this high-risk subpopulation, but other risk factors have not been consistently defined. Some patients with anxiety disorders and insomnia may be vulnerable (Griffiths and Weerts, 1997). The present study followed up subjects for an average of one year. Longer follow-up times are needed to assess whether subjects with high dose dependence or concomitant alcohol problems are able to maintain their dose reductions.

Subjects in this study did not do better after gradual tapering with cognitive-behavioral treatment when compared with standard treatment. Previous research has shown that cognitive-behavioral treatment is generally effective for substance use (Donovan et al., 1994; Irvin et al., 1999; Koski-Jännes, 1999; Kadden, 2001). Generally, psychotherapies are more effective than a no-treatment condition, but consistently identifying different treatment effects between various forms of active treatments has been difficult (Carroll, 1996; Project MATCH Research Group, 1997; Wampold et al., 1997). Studies have thus far been unable to prove cognitive-behavioral therapy superior to conventional treatment (Carroll, 1996). One randomized study evaluating the effectiveness of cognitive-behavioral treatment in community settings found that routine care gave results comparable with manual guided high standardization cognitive-behavioral treatment and "clinical judgment"-based low standardization cognitive-behavioral treatment delivered by trained therapists (Morgenstern et al., 2001). Because different treatments have appeared to lead to equivalent outcomes, it has been suggested that more attention be given to therapist effects (Crits-Christoph et al., 1991; Connors et al., 1997), to the necessary and sufficient elements of effective substance abuse treatment, perhaps shared by different kinds of therapy (Morgenstern et al., 2001), and to the basic change processes in addiction (Orford, 2002). Previous research has been unable to consistently identify the patient and treatment variables and processes mediating treatment outcomes (Project MATCH Research Group, 1997b). As many combinations of patient and treatment factors are likely to lead to the same result, it has also been suggested that future research focus on the extremes to determine the treatment modalities optimal for different patient groups (Moyer et al., 2001). In the present study, the reason for not finding any differences between the two treatment conditions probably lies in the above-mentioned

factors, although heterogeneity of study subjects and overlap in treatment approaches may also have affected the probability of finding differences between study groups.

It has been argued that during withdrawal treatment patients should learn alternative ways of coping with possible withdrawal symptoms and anxiety that result when medication ceases. Underlying psychiatric disorders should simultaneously be alleviated. Psychological treatment should address both of these components (Spiegel, 1999). There are also considerations concerning combination of BZs and cognitive therapy. BZs do not seem to inhibit gains made from cognitive-behavioral therapy during acute treatment, but some evidence suggests that they may undermine post-treatment outcome (Spiegel and Bruce, 1997; Fava et al., 2001a, 2001b) and long-term outcome (van Balkom et al., 1996). This effect was seen in a study where relatively high doses of BZs were discontinued after completion of cognitive-behavioral therapy (Marks et al., 1993). During a six-month follow-up, patients who had received alprazolam medication (mean final dose 5.8 mg/day) deteriorated more often than those who had received placebo. In studies using lower doses of BZs, cognitive-behavioral therapy clearly offered more protection from relapse after BZ discontinuation (Bruce et al., 1999). In animals, a state-dependent learning phenomenon has been observed with many substances that have fear-reducing properties, including BZs. According to the state-dependent learning theory, therapeutic gains achieved under the influence of a drug are not transferred to the subsequent drug-free state. This phenomenon is dose-dependent. In humans, state-dependent learning, in addition to cognitive factors, has been hypothesized to have an effect on relapses after BZ discontinuation (Spiegel and Bruce, 1997). However, observations have also been made of concurrent BZ treatment not affecting outcome of behavior therapy (Wardle et al., 1994). Furthermore, timing of cognitive therapy may be important when discontinuing BZ treatment (Spiegel, 1999). Previous research has found some evidence that panic disorder patients do better after withdrawal treatment combined with cognitive therapy, when the therapy is designed to continue after BZ cessation (Spiegel, 1999). Accordingly, BZ withdrawal treatment in subjects initially using high doses could be more effective if cognitive-behavioral therapy were to begin after some dose reductions have already been made and to continue after the drug is discontinued altogether.

In the present study, the median duration of treatment was 32.0 (range 0-52) weeks for the experimental group and 36.6 (range 0-52) weeks for the control group. Those who were able to discontinue BZs during treatment received treatment for a median of 29.7 (range 4.4-39.9) weeks. In the literature, scant data are available on the efficacy of different BZ withdrawal timeframes (Higgitt et al., 1985; Lader and Morton, 1991; Marriot and Tyrer, 1993; Roy-Byrne and Ballenger, 1993; Ashton, 1994). Short four-week withdrawal treatments have been criticized for leading to high dropout rates (Schweizer et al., 1990; Rickels et al., 1993) (see also section 2.4.2.). A 10-week period seems to be better tolerated (Cantopher et al., 1990). For subjects using supratherapeutic BZ dosages, data on the optimal duration of treatment are lacking.

Clinical experience indicates that the first 50% of BZ taper can usually be completed in a few weeks, while the remaining 50% takes much longer (Rickels et al., 1999). On the other hand, an excessively long treatment may become the focus of anxiety, adding to the total amount of distress (Lader and Morton, 1991; Ashton, 1994). The most recent recommendations on BZ taper for chronic therapeutic dose users, based on clinical experience, include establishing a stable relationship between the patient and therapist, treating any underlying psychiatric disorders first, initiating BZ taper only after the patient's psychopathology levels have been reduced, and maintaining a reduced BZ dose for several months before the final taper attempt is initiated (Rickels et al., 1999).

6.4. Alcohol use

During the withdrawal treatment no changes in subjects' AUDIT scores or GGT levels occurred, but 23% of experimental group participants and 37% of controls reported less frequent alcohol consumption than at the beginning of the study. At the end of the follow-up phase, 30% of experimental group subjects and 32% of controls reported a decrease in alcohol consumption frequency compared with pre-treatment levels; no median change occurred in AUDIT or GGT values. Overall, study subjects' alcohol consumption did not appear to change appreciably compared with pre-treatment levels. The subjects with clinically significant reductions in benzodiazepine use also did not modify their alcohol use markedly, as defined by average AUDIT scores and GGT values as well as interviews regarding drinking frequency. However, the highest alcohol consumption at the end of the follow-up was found in the group that was least successful with BZ withdrawal, i.e. those who did not decrease their BZ doses or decreased by no more than 50%. Therefore, while reductions in BZ doses appeared to be unrelated to increased alcohol consumption, failure in BZ withdrawal might be related.

6.5. Psychiatric disorders

The findings that nearly all subjects had at least one additional lifetime axis I disorder diagnosed and that nearly 80% had current axis I diagnoses were consistent with previous data of BZ-dependent inpatients (Busto et al., 1996) and outpatients (Romach et al., 1995; Martínez-Cano et al., 1999). Personality disorders were detected in 64% of subjects. Cluster C personality disorder diagnoses were the most prevalent (47%), followed by cluster B diagnoses (26%), 75% of which were borderline personality disorders. Psychiatric diagnoses other than cluster B personality disorder were not associated with outcome. The impact of personality characteristics typical of cluster B personality disorders has not been investigated in previous research, while cluster C personality characteristics have been studied extensively (Rickels et al., 1988, 1990; Holton et al., 1992; Schweizer et al., 1998). In the present study, none of the 20 subjects (26% of study sample) with cluster B personality disorders succeeded in discontinuing BZ use during treatment. During follow-up four subjects with a cluster B personality disorder had BZ-free episodes, but only one subject who continued to receive intensive treatment managed to discontinue BZ use and thereafter stay BZ-free. Initial BZ doses or other predictors of BZ discontinuation did not explain this. Cluster B personality was associated with dropping out of treatment. Cluster B personality was not, however, associated with follow-up outcome. To be able to reliably evaluate the impact of personality on long-term outcome of BZ discontinuation treatment, a larger subject sample is needed. However, our finding is supported by previous observations that patients with impulsive personality characteristics may exhibit a greater severity of depressive and anxiety symptoms than persons with other or no personality disorders (Comtois et al., 1999) and may be at risk for dropping out of psychotherapy (Perry et al., 1999) or treatment for alcohol dependence (Kravitz et al., 1999).

6.6. Psychopathology measures

During the study, subjects' psychopathology scores and several quality of life scores improved significantly. Because 91% of subjects were physically dependent on BZs, they may have been experiencing withdrawal symptoms while using them. This is consistent with 49% of subjects at baseline being diagnosed with current anxiety disorders, while 92% reported current use of BZs to treat symptoms of anxiety.

No consensus exists about which patients remaining symptomatic during continued BZ administration will benefit from drug discontinuation and which need more effective pharmacotherapy, and how to discriminate between these two groups (Woods et al., 1992; Rickels et al., 2000). The present study indicated that the subjects who decreased BZ use more also had greater improvements in their levels of psychiatric symptoms and quality of life. The scores also improved for subjects diagnosed with a current panic disorder, agoraphobia, or social phobia, indicating that these individuals either benefited from the study treatments or were experiencing withdrawal anxiety when entering the study. This suggests that for all chronic BZ users, including those with anxiety disorders, the need for BZ discontinuation or dose decrease should be considered.

6.7. Predictors of discontinuing benzodiazepines and staying benzodiazepine-free

Lower initial doses of BZs and no previous withdrawal experience predicted successful discontinuation of BZs and a BZ-free outcome through the follow-up. High life satisfaction also predicted a successful long-term outcome. Life satisfaction score was associated with anxiety score and with several other measures of psychopathology so life satisfaction may have reflected anxiety levels, or more broadly, psychopathology levels. Higher BZ dose and previous withdrawal attempts were related to a higher level of dependence in terms of SDS scores and to more BZ dependence criteria being met, indicating that the relationships of initial BZ dose and previous withdrawal attempts to outcome could be partly explained by the severity of dependence.

Other psychiatric diagnoses or levels of psychopathology were unrelated to BZ discontinuation. This finding is consistent with some earlier studies (Schweizer et al., 1990; Charney et al., 2000), but contradicts others (Rickels et al., 1993, 2000). Charney et al. (2000) speculated that the pharmacological and psychological interventions that they used possibly mitigated the impact of psychopathology on outcome. In the present study, it is possible that the use of fluoxetine for treatment of depression had an effect. It is also possible that the treatment aimed at BZ discontinuation simultaneously helped to reduce anxiety. Alcohol-related variables also did not predict outcome. One explanation is that subjects with alcohol use disorders were similar to the others with respect to the factors predicting outcome. Another explanation may be that the treatments alleviated the subjects' alcohol problems.

6.8. Conclusions

1. Subjects with complicated BZ dependence fared no better after gradual tapering with cognitive-behavioral treatment than with treatment-as-usual.

2. The findings that nearly all study subjects had at least one additional lifetime axis I disorder diagnosis and that 80% had current axis I diagnoses were consistent with previous data on BZ-dependent patients. Personality disorders were detected in 64% of subjects. Subjects with BZ dependence appear to have a high prevalence of various psychiatric disorders. Thus, subpopulations of patients with BZ dependence should be defined to enable optimal treatment modalities to be chosen.

3. Lower BZ dose and lack of previous withdrawal attempts predicted successful outcome, and higher life satisfaction predicted remaining BZ-free. The relations of initial BZ dose and previous withdrawal attempts to outcome seemed to be at least partly explained by the severity of dependence. No subjects with cluster B personality disorders succeeded in stopping BZ use during the treatment, and only one subject managed to discontinue BZ use during the follow-up. In addition, cluster B personality was associated with dropping out of treatment. While these findings are preliminary, they do indicate that the need to further investigate predictors of successful BZ discontinuation in different populations exists. One treatment implication of this study is that patients with cluster B personality/borderline personality disorder and BZ dependence may require treatment for their personality disorders to benefit from BZ withdrawal treatment.

4. The results of BZ withdrawal treatment were maintained in both treatment groups and were comparable with those of follow-up studies in subjects with less complicated dependence. Subjects with high pre-taper BZ doses generally managed to lower their usage to therapeutic levels. The findings suggest that patients with complicated BZ dependence may benefit from outpatient BZ discontinuation treatment to achieve dose reduction to therapeutic levels. However, further research is needed to obtain information on more effective treatments.

5. All measurements for subjects with clinically significant (over 50%) BZ dose decreases tended to improve more than those for subjects with smaller decreases, and some differences in the HRQOL scores were significant. Therefore, in subjects with complicated BZ dependence, clinically significant dose decreases are associated with improvements in self-rated quality of life.

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